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(54) **REMEDIES FOR DEPRESSION CONTAINING EP1 ANTAGONIST AS THE ACTIVE  
INGREDIENT**

(57) A pharmaceutical composition for the treatment  
and/or prevention of depression comprising a com-  
pound having an antagonistic activity for EP<sub>1</sub> receptor  
which a prostaglandin E<sub>2</sub> receptor subtype.  
EP<sub>1</sub> antagonist is useful for the treatment of depres-

sion, for example, endogenous depression, reactive de-  
pression, weatherability depression, neurological de-  
pressed state, the depressed state of brain organic  
mental disorder.

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## Description

## Technical Field

- 5 [0001] The present invention relates to a pharmaceutical composition for the treatment of depression comprising the EP<sub>1</sub> antagonist as active ingredient.

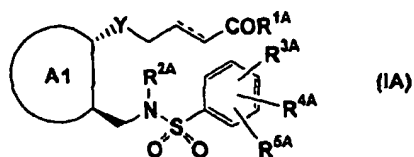
## Background

- 10 [0002] Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) has been known as a metabolite in the arachidonic acid cascade. It has been known that PGE<sub>2</sub> possesses cyto-protective activity, uterine contractile activity, a pain-inducing effect, a promoting effect on digestive peristalsis, an awaking effect, a suppressive effect on gastric acid secretion, hypotensive activity, and diuretic activity.
- [0003] In the recent study, it was found that PGE<sub>2</sub> receptor was divided into some subtypes, which possesses different physical roles from each other. At present, four receptor subtypes are known and they are called EP<sub>1</sub>, EP<sub>2</sub>, EP<sub>3</sub> and EP<sub>4</sub> respectively [Negishi M. et al, J. Lipid Mediators Cell Signaling 12 379-391 (1995)].
- 15 [0004] PGE<sub>2</sub> has a broad range of a physiologically active, therefore it has a fault that an activity other than a purpose will become a side effect. However, it has been studied to overcome the fault by a research of each subtype role and a synthesis of compounds having an effective action for one subtype only.
- 20 [0005] Among these subtypes, it is known that EP<sub>1</sub> subtype relates to pain, fever, diuresis [Br. J. Pharmacol., 112, 735-40 (1994); European J. Pharmacol., 152, 273-279 (1988); Gen Pharmacol., Sep 1992, 23(5), 805-809]. Therefore, it is believed that an antagonism for this receptor is useful as analgesics, antipyretic or a therapeutic agent of frequent urination.
- [0006] Besides, it is known that EP<sub>1</sub> antagonists have an inhibitory activity of a formation of abnormal crypt in the lining of the large intestine and polyp in the intestine, and show an anticancer activity [see reference WO 00/69465].
- 25 [0007] Depression is led by various factors, and the pathological physiology is remained incompletely understood. Monoamine reuptake inhibitor and monoamine oxidase (MAO) inhibitor are showed an antidepressive activity, and it is considered that an abnormal mono-aminergic neuron system plays a role in the development of depression.
- [0008] As an antidepressant, MAO inhibitors including hydrazine derivatives, emotion stimulators such as a reuptake inhibitor of noradrenaline (NA) and 5-hydroxytryptamine (5-HT), emotion regulators including benzodiazepine derivatives and psychostimulants including Meratoran are known. Then, MAO inhibitors are not used because of a serious hepatopathy and hypertensive crisis, and new type reuptake inhibitor of NA and 5-HT are used, that they are improved side effects such as dry mouth, drowsiness, dizziness, urinary disturbance that are side effects of tricyclic antidepressants as typified by imipramine.
- 30 [0009] On the other hand, it was not confirmed by an experiment that a relationship of EP<sub>1</sub> receptors and depression and antidepressive activity of EP<sub>1</sub> antagonist.

## Disclosure of the Invention

- 40 [0010] Energetic investigations about a role of EP<sub>1</sub> receptors in the brain by various experiments using EP<sub>1</sub> antagonists have been carried out. The present inventors have found that EP<sub>1</sub> antagonists have an antidepressive activity and accomplished the present invention. As mentioned above, it was known that an increase of dopamine in the brain on EP<sub>1</sub> receptor knockout mouse, however, it was not confirmed whether EP<sub>1</sub> antagonists have an antidepressive activity.
- 45 [0011] The present invention relates to a pharmaceutical composition for the treatment and/or prevention of depression, such as endogenous depression, reactive depression, weatherability depression, neurological depressed state, the depressed state of brain organic mental disorder, comprising an antagonist for EP<sub>1</sub> receptor, which is one subtype of PGE<sub>2</sub> receptor.
- [0012] EP<sub>1</sub> antagonists of the present invention bond to EP<sub>1</sub> receptor, which is a subtype of PGE<sub>2</sub> receptor, and show an antagonistic action. More preferably EP<sub>1</sub> antagonists are specifically bond to EP<sub>1</sub> receptor and show an antagonistic action.
- 50 [0013] Known EP<sub>1</sub> antagonists and any EP<sub>1</sub> antagonists, which will be found in the future, are included in EP<sub>1</sub> antagonists of the present invention.
- [0014] Any EP<sub>1</sub> antagonists are preferable and more preferable EP<sub>1</sub> antagonists are, for example,

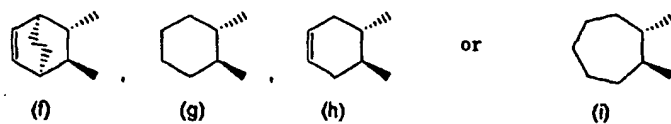
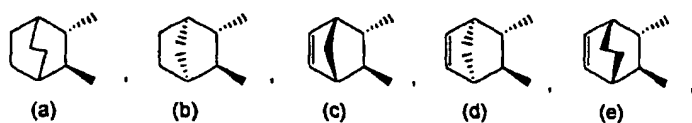
- 55 (1) in the specification of EP 878465, the compound of formula (IA)



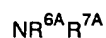
wherein



is



R<sup>1A</sup> is hydroxy, C1-4 alkoxy or a group of formula



in which R<sup>6A</sup> and R<sup>7A</sup> each independently, is hydrogen or C1-4 alkyl,

R<sup>2A</sup> is hydrogen or C1-4 alkyl,

R<sup>3A</sup> and R<sup>4A</sup> are C1-4 alkyl, halogen atom or trifluoromethyl,

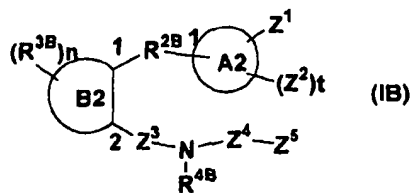
R<sup>5A</sup> is hydrogen, C1-4 alkyl, halogen atom or trifluoromethyl,

Y is cis-vinylene or trans-vinylene

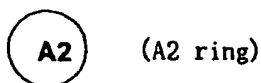
is a single bond or a double bond:

a non-toxic salt thereof or a cyclodextrin clathrate thereof;

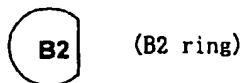
(2) in the specification of WO 98/27053, the compound of formula (IB)



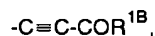
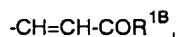
wherein



and



each independently, is C5-15 carbocyclic ring or 5-7 membered heterocyclic ring containing 1 or 2 of oxygens, sulfurs or nitrogens, Z<sup>1</sup> is



in which R<sup>1B</sup> is hydroxy, C1-4 alkoxy or NR<sup>6B</sup>R<sup>7B</sup> in which R<sup>6B</sup> and R<sup>7B</sup> each independently, is hydrogen or C1-4 alkyl; or



Z<sup>2</sup> is hydrogen, C1-4 alkyl, C1-4 alkoxy, nitro, halogen atom, trifluoromethyl, trifluoromethoxy, hydroxy or COR<sup>1B</sup> in which R<sup>1B</sup> as hereinafter defined;

Z<sup>3</sup> is a single bond or C1-4 alkylene,

Z<sup>4</sup> is SO<sub>2</sub> or CO,

Z<sup>5</sup> is (1) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl, (2) phenyl, C3-7 cycloalkyl or 5-7 membered heterocyclic ring containing 1-2 of oxygens, sulfurs or nitrogens, (3) C1-4 alkyl, C2-4 alkenyl or C2-4 alkynyl substituted by phenyl or C3-7 cycloalkyl,

in the above (2) and (3), phenyl, C3-7 cycloalkyl and 5-7 membered heterocyclic ring containing 1-2 of oxygens, sulfurs or nitrogens may be substituted by 1-5 of R<sup>5B</sup> in which multiple R<sup>5B</sup> each independently, is hydrogen, C1-6 alkyl, C1-6 alkoxy, C1-6 alkylthio, nitro, halogen atom, trifluoromethyl, trifluoromethoxy or hydroxy;

R<sup>2B</sup> is CONR<sup>8B</sup>, NR<sup>8B</sup>CO, CONR<sup>8B</sup>-C1-4 alkylene, C1-4 alkylene-CONR<sup>8B</sup>, NR<sup>8B</sup>CO-C1-4 alkylene, C1-4 alkylene-NR<sup>8B</sup>CO, C1-3 alkylene-CONR<sup>8B</sup>-C1-3 alkylene, C1-3 alkylene-NR<sup>8B</sup>CO-C1-3 alkylene, in which R<sup>8B</sup> is hydrogen or C1-4 alkyl; oxygen, sulfur, NZ<sup>6</sup> in which Z<sup>6</sup> is hydrogen or C1-4 alkyl; -Z<sup>7</sup>-C1-4 alkylene, C1-4 alkylene-Z<sup>7</sup>, C1-3 alkylene-Z<sup>7</sup>-C1-3 alkylene in which Z<sup>7</sup> is oxygen, sulfur or NZ<sup>6</sup> in which Z<sup>6</sup> is as hereinbefore defined; CO, CO-C1-4 alkylene, C1-4 alkylene-CO, C1-3 alkylene-CO-C1-3 alkylene, C2-4 alkylene, C2-4 alkenylene, C2-4 alkynylene,

R<sup>3B</sup> is hydrogen, C1-6 alkyl, C1-6 alkoxy, C1-6 alkylthio, nitro, halogen atom, trifluoromethyl, trifluoromethoxy, hydroxy or hydroxymethyl,

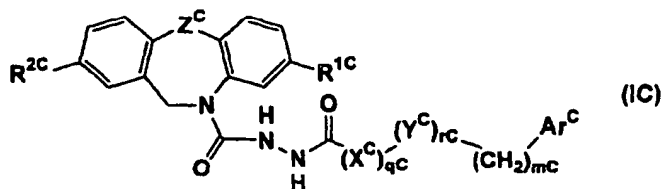
R<sup>4B</sup> is (1) hydrogen, (2) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl, (3) C1-6 alkyl substituted by 1-2 of COOZ<sup>8</sup>, CONZ<sup>9</sup>Z<sup>10</sup>, OZ<sup>8</sup> in which Z<sup>8</sup>, Z<sup>9</sup> and Z<sup>10</sup> each independently, is hydrogen or C1-4 alkyl; and C1-4 alkoxy-C1-4 alkoxy, (4) C3-7 cycloalkyl, (5) C1-4 alkyl, C2-4 alkenyl or C2-4 alkynyl substituted by phenyl or C3-7 cycloalkyl, in the above (4) and (5), phenyl, C3-7 cycloalkyl may be substituted by 1-5 of R<sup>5B</sup> in which R<sup>5B</sup> is as hereinbefore defined,

n and t each independently, is 1-4,

with the proviso that (1) R<sup>2B</sup> bond to atom of only 1-position in B<sup>2</sup> ring and R<sup>3B</sup> bond to atom of only 2-position in B<sup>2</sup> ring,

(2) when A<sup>2</sup> ring is benzene and (Z<sup>2</sup>)<sub>t</sub> is not COR<sup>18</sup>, then Z<sup>1</sup> bond only 3 or 4-position in benzene of A<sup>2</sup> ring;

(3) in the specification of WO 92/19617, the compound of formula (IC)



wherein R<sup>1C</sup> is hydrogen, halogen atom or —CF<sub>3</sub>,

R<sup>2C</sup> is hydrogen, halogen atom, —OH or —OCH<sub>3</sub>,

Z<sup>C</sup> is oxygen, sulfur, —S(O)— or —S(O)<sub>2</sub>—,

X<sup>C</sup> is —CH=CH—, —CF<sub>2</sub>—, —CHF—, —(CH<sub>2</sub>)<sub>mc</sub>— or —(CH<sub>2</sub>)<sub>mc</sub>—CH=CH—,

Y<sup>C</sup> is —CH(OH)—, —NR<sup>3C</sup>—, sulfur, —S(O)—, —S(O)<sub>2</sub>— or oxygen,

q<sup>C</sup> is 0 or 1,

r<sup>C</sup> is 0 or 1, with the proviso that in the case of following (1), (2) or (3), r<sup>C</sup> is not 0:

(1) X<sup>C</sup> is —CH=CH—, —(CH<sub>2</sub>)<sub>nc</sub>— or —(CH<sub>2</sub>)<sub>pc</sub>—CH=CH—, q<sup>C</sup> is 1 and Ar<sup>C</sup> is imidazole or phenyl,

(2) X<sup>C</sup> is —(CH<sub>2</sub>)<sub>nc</sub>—, q<sup>C</sup> is 1, n<sup>C</sup> is 1 and Ar<sup>C</sup> is ethylphenyl substituted by halogen atom, methyl or alkoxy,

(3) q<sup>C</sup> is 1, m<sup>C</sup> is 1, 2, 3, 4, 5 or 6 and Ar<sup>C</sup> is imidazole or phenyl,

m<sup>C</sup> is 0-6, with the proviso that when X<sup>C</sup> is —(CH<sub>2</sub>)<sub>nc</sub>—, q<sup>C</sup> is 1, Y<sup>C</sup> is oxygen, sulfur, —S(O)— or —S(O)<sub>2</sub>— and Ar<sup>C</sup> is phenyl, and then m<sup>C</sup> is not 0,

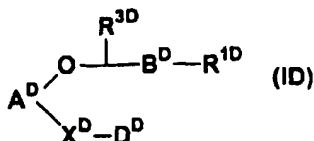
n<sup>C</sup> is 1-6,

p<sup>C</sup> is 1-6,

R<sup>3C</sup> is hydrogen or t-butyloxycarbonyl,

Ar<sup>C</sup> is aryl, alkyl-substituted aryl or aryl-substituted aryl;

(4) in the specification of WO 96/06822, the compound of formula (ID)



wherein A<sup>D</sup> is an optionally substituted: 8-10 membered bicyclic heteroaryl, 5-6 membered heteroaryl, naphthyl or phenyl, with the proviso that —OCH(R<sup>3D</sup>)— and —X<sup>D</sup>— linking group are positioned in a 1, 2 relationship to one another on ring carbon atoms,

B<sup>D</sup> is an optionally substituted 5-6 membered heteroaryl ring system or optionally substituted phenyl,

D<sup>D</sup> is optionally substituted: pyridyl, pyrazinyl, pyrimidyl, pyridazyl, pyrrolyl, thienyl, furyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl or phenyl,

X<sup>D</sup> is —(CHR<sup>4D</sup>)<sub>n<sup>D</sup></sub>— or —(CHR<sup>4D</sup>)<sub>p<sup>D</sup></sub>CR<sup>4D</sup>=CR<sup>4D</sup>(CHR<sup>4D</sup>)<sub>q<sup>D</sup></sub>—, in which n<sup>D</sup> is 1-3, and p<sup>D</sup> and q<sup>D</sup> are either both 0 or one of p<sup>D</sup> and q<sup>D</sup> is 1 and the other is 0,

R<sup>1D</sup> is positioned on ring B<sup>D</sup> in a 1, 3 or 1, 4 relationship with the —OCH(R<sup>3D</sup>)— linking group in 6-membered rings and in a 1, 3 relationship with —OCH(R<sup>3D</sup>)— linking group in 5-membered rings and carboxy, carboxy-C1-3 alkyl, tetrazolyl, tetrazolyl-C1-3 alkyl, tetrionic acid, hydroxamic acid or sulphonic acid, or

R<sup>1D</sup> is —CONR<sup>aD</sup>R<sup>a1D</sup> in which R<sup>aD</sup> is hydrogen or C1-6 alkyl, R<sup>a1D</sup> is hydrogen, or optionally substituted C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-7 cycloalkyl, C3-7 cycloalkyl-C1-6 alkyl, C3-7 cycloalkyl-C2-6 alkenyl, C3-7 cycloalkyl-C2-6 alkynyl, C5-7 cycloalkenyl, C3-7 cycloalkenyl-C1-6 alkyl, C5-7 cycloalkenyl-C2-6 alkenyl, C5-7

cycloalkenyl-C2-6 alkynyl, C1-3 alkyl substituted by 5-6 membered saturated or partially saturated heterocyclic ring, 5-6 membered saturated or partially saturated heterocyclic ring or 5-6 membered heteroaryl, or  $R^{aD}$  and  $R^{a1D}$  together with the amide nitrogen to which they are attached ( $NR^{aD}R^{a1D}$ ) form an amino acid residue or ester thereof, or

$R^{1D}$  is  $—CONHSO_2R^{bD}$  in which  $R^{bD}$  is optionally substituted C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-7 cycloalkyl-C1-6 alkyl, C3-7 cycloalkyl-C2-6 alkenyl, C3-7 cycloalkyl-C2-6 alkynyl, C3-7 cycloalkenyl-C1-6 alkyl, C3-7 cycloalkenyl-C2-6 alkenyl, C3-7 cycloalkenyl-C2-6 alkynyl, 5-6 membered heteroaryl, 5-6 membered heteroaryl-C1-6 alkyl, phenyl, phenyl-C1-6 alkyl, 5-6 membered saturated or partially saturated heterocyclic ring or 5-6 membered saturated or partially saturated heterocyclic ring-C1-6 alkyl,

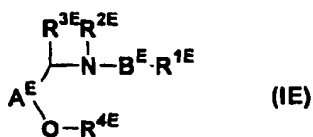
$R^{3D}$  is hydrogen or C1-4 alkyl,

$R^{4D}$  is hydrogen or C1-4 alkyl,

with the proviso that 4-(2-benzyl-3-hydroxy-4-formylphenoxy-methyl)-3-methoxybenzoic acid and 4-(2-(3-phenyl-prop-2-ene-1-yl)-3-hydroxy-4-formylphenoxy-methyl)-3-methoxybenzoic acid are excluded;

or N-oxide thereof, or S-oxide of sulfur containing rings, or a pharmaceutically acceptable salt thereof or in vivo hydrolyzable ester or amide thereof,

(5) in the specification of WO 97/00863, the compound of formula (IE)



wherein  $A^E$  is optionally substituted: phenyl, naphthyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidyl, thienyl, thiazolyl, oxazolyl or thiadiazolyl having at least two adjacent ring carbon atoms, with the proviso that  $—CH(R^{3E})N(R^{2E})B^E$ .  $R^{1E}$  and  $—OR^{4E}$  are positioned in a 1, 2 relationship to one another on ring carbon atom and the ring atom position ortho to the  $OR^{4E}$  linking group (and therefor in the 3-position relative to the  $—CH(R^{3E})N(R^{2E})$  linking group) is not substituted,

$B^E$  is optionally substituted: phenyl, pyridyl, thiazolyl, oxazolyl, thienyl, thiadiazolyl, imidazolyl, pyrazinyl, pyridazinyl or pyrimidyl,

$R^{1E}$  is positioned on ring  $B^E$  in a 1, 3 or 1, 4 relationship with  $—CH(R^{3E})N(R^{2E})$  linking group and is carboxy, carboxy-C1-3 alkyl, tetrazolyl, tetrazolyl-C1-3 alkyl, *tetronic acid*, hydroxamic acid, sulphonic acid, or

$R^{1E}$  is  $—CONR^{aE}R^{a1E}$  in which  $R^{aE}$  is hydrogen or C1-6 alkyl,  $R^{a1E}$  is hydrogen, C1-6 alkyl (optionally substituted by halogen atom, amino, C1-4 alkylamino, di-C1-4 alkylamino, hydroxy, nitro, cyano, trifluoromethyl, C1-4 alkoxy or C1-4 alkoxy-carbonyl), C2-6 alkenyl (the double bond is not in the 1-position), C2-6 alkynyl (the triple bond is not in the 1-position), carboxyphenyl, 5-6 membered heterocyclyl-C1-3 alkyl, 5-6 membered heteroaryl-C1-3 alkyl, 5-6 membered heterocyclyl or 5-6 membered heteroaryl, or  $R^{aE}$  and

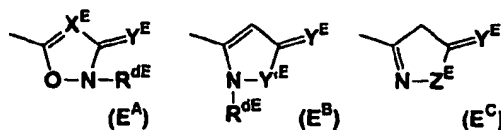
$R^{a1E}$  together with the amide nitrogen to which they are attached ( $NR^{aE}R^{a1E}$ ) form an amino acid residue or ester thereof, or

$R^{1E}$  is  $—CONHSO_2R^{bE}$  in which  $R^{bE}$  is C1-6 alkyl (optionally substituted by halogen atom, hydroxy, nitro, cyano, trifluoromethyl, C1-4 alkoxy, amino, C1-4 alkylamino, di-C1-4 alkylamino or C1-4 alkoxy-carbonyl), C2-6 alkenyl (the double bond is not in the 1-position), C2-6 alkynyl (the triple bond is not in the 1-position), 5-6 membered heterocyclyl-C1-3 alkyl, 5-6 membered heteroaryl-C1-3 alkyl, 5-6 membered heterocyclyl or 5-6 membered heteroaryl or phenyl,

wherein any heterocyclyl or heteroaryl group in  $R^{a1E}$  is optionally substituted by halogen atom, hydroxy, nitro, amino, cyano, C1-6 alkoxy, C1-6 alkyl-S( $O$ ) $_p$  ( $p^E$  is 0, 1 or 2), C1-6 alkylcarbamoyl, C1-4 alkylcarbamoyl, di(C1-4 alkyl)carbamoyl, C2-6 alkenyl, C2-6 alkynyl, C1-4 alkoxy-carbonylamino, C1-4 alkanoylamino, C1-4 alkanoyl (N-C1-4 alkyl)amino, C1-4 alkanesulfonamide, benzenesulfonamide, aminosulfonyl, C1-4 alkylaminosulfonyl, di(C1-4 alkyl)aminosulfonyl, C1-4 alkoxy-carbonyl, C-4 alkanoyloxy C1-6 alkanoyl, formyl-C1-4 alkyl, hydroxyimino-C1-6 alkyl, C1-4 alkoxyimino-C1-6 alkyl or C1-6 alkylcarbamoylamino, or

$R^{1E}$  is  $—SO_2N(R^{cE})R^{c1E}$  in which  $R^{cE}$  is hydrogen or C1-4 alkyl and  $R^{c1E}$  is hydrogen or C1-4 alkyl, or

$R^{1E}$  is the formula ( $E^A$ ), ( $E^B$ ) or ( $E^C$ ):



wherein  $X^E$  is CH or nitrogen,

$Y^E$  is oxygen or sulfur,

$Y^E$  is oxygen or  $NR^{dE}$  and

$Z^E$  is  $CH_2$ ,  $NR^{dE}$  or oxygen, with the proviso that there is no more than one ring oxygen and there are at least two ring heteroatoms and wherein  $R^{dE}$  is hydrogen or C1-4 alkyl,

$R^{2E}$  is hydrogen, C1-6 alkyl optionally substituted by hydroxy, cyano or trifluoromethyl, C2-6 alkynyl (the double bond is not in the 1-position), C2-6 alkynyl (the triple bond is not in the 1-position), phenyl-C1-3 alkyl or pyridyl-C1-3 alkyl,

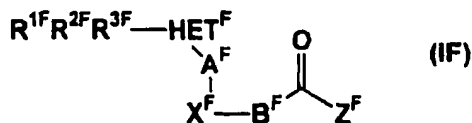
$R^{3E}$  is hydrogen, methyl or ethyl,

$R^{4E}$  is optionally substituted: C1-6 alkyl, C3-7 cycloalkyl-C1-3 alkyl or C3-7 cycloalkyl,

with the proviso that 2-[2-methoxybenzylamino]pyridine-5-carboxylic acid, 4-[2-methoxybenzylamino]benzoic acid, 5-[2, 3-dimethoxybenzylamino]-2-chloro-3-aminosulfonylbenzoic acid and 5-[2,5-dimethoxybenzylamino]-2-hydroxybenzoic acid are excluded;

or N-oxide of  $—NR^{2E}$ , or S-oxide of sulfur containing rings, or a pharmaceutically acceptable salt thereof or in vivo hydrolyzable ester or amide thereof;

(6) in the specification of WO 99/47497, the compound of formula (IF)



wherein  $HET^F$  is 5-12 membered mono- or bi-cyclic aromatic ring containing 0-3 heteroatoms selected from oxygen,  $S(O)_{nF}$  and  $N(O)_{mF}$ , in which  $m^F$  is 0 or 1,  $n^F$  is 0, 1 or 2,  $A^F$  is  $—W^F$ ,  $—C(O)–$ ,  $—C(R^{7F})–W^F$ ,  $—W^F–C(R^{7F})_2–$ ,  $—CR^{7F}(OR^{20F})–$ ,  $—C(R^{7F})_2–$ ,  $—C(R^{7F})_2–C(OR^{20F})R^{7F}$ ,  $—C(R^{7F})_2–C(R^{7F})_2–$  or  $—CR^{7F}=CR^{7F}$ , in which  $W^F$  is oxygen,  $S(O)_{nF}$  or  $NR^{17F}$ ,

$X^F$  is 5-10 membered mono- or bi-cyclic aryl or heteroaryl having 1-3 heteroatoms selected from oxygen,  $S(O)_{nF}$  and  $N(O)_{mF}$ , and optionally substituted by  $R^{14F}$  and  $R^{15F}$ , and  $A^F$  and  $B^F$  are attached to the aryl or heteroaryl ortho relative to each other,

$Y^F$  is O,  $S(O)_{nF}$ ,  $NR^{17F}$ , a bond or  $—CR^{18F}=CR^{18F}$ ;

$B^F$  is  $—(C(R^{18F})_2)_{pF}–Y^F–C(R^{18F})_2–qF–$ , in which  $p^F$  and  $q^F$  are independently 0-3, such that when  $Y^F$  is O,  $S(O)_{nF}$ ,  $NR^{17F}$  or  $—CR^{18F}=CR^{18F}$ ,  $p^F+q^F$  is 0-6, and when  $Y^F$  is a bond,  $p^F+q^F$  is 1-6;

$Z^F$  is OH,  $NHSO_2R^{19F}$ ;

$R^{1F}$ ,  $R^{2F}$  and  $R^{3F}$  each independently, is hydrogen, halogen atom, lower alkyl, lower alkenyl, lower alkynyl, lower alkenyl- $HET^F(R^{4F})_{4,9}$ ,  $—(C(R^{4F})_2)_{pF}SR^{5F}$ ,  $—(C(R^{4F})_2)_{pF}OR^{8F}$ ,  $—(C(R^{4F})_2)_{pF}N(R^{6F})_2$ , CN,  $NO_2$ ,  $—(C(R^{4F})_2)_{pF}C(R^{7F})_3$ ,  $—COOR^{9F}$ ,  $—CON(R^{6F})_2$  or  $—(C(R^{4F})_2)_{pF}S(O)_{nF}R^{10F}$ ,

each  $R^{4F}$  is hydrogen, F,  $CF_3$ , lower alkyl or

two  $R^{4F}$ , taken together, is a ring of up to six atoms, optionally containing one heteroatom selected from O,  $S(O)_{nF}$  and  $N(O)_{mF}$ ,

each  $R^{5F}$  is independently lower alkyl, lower alkenyl, lower alkynyl,  $CF_3$ , lower alkyl- $HET^F$ , lower alkenyl- $HET^F$ ,  $—(C(R^{18F})_2)_{pF}Ph(R^{11F})_{0,2}$ ,

each  $R^{6F}$  is independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl,  $CF_3$ , Ph, Bn or two  $R^{6F}$  together with N to which they are attached, is a ring of up to six atoms, optionally containing an additional heteroatom selected from O,  $S(O)_{nF}$  and  $N(O)_{mF}$ ,

each  $R^{7F}$  is independently hydrogen, F,  $CF_3$ , lower alkyl, or two  $R^{7F}$  taken together, is 3-6 membered aromatic or aliphatic ring containing 0-2 heteroatom selected from O,  $S(O)_{nF}$  and  $N(O)_{mF}$ ,

each  $R^{8F}$  is hydrogen or  $R^{5F}$ ,

each R<sup>9F</sup> is independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, Ph or Bn,  
 each R<sup>10F</sup> is independently lower alkyl, lower alkenyl, lower alkynyl, CF<sub>3</sub>, Ph(R<sup>11F</sup>)<sub>0-3</sub>, CH<sub>2</sub>Ph(R<sup>11F</sup>)<sub>0-3</sub> or N(R<sup>6F</sup>)<sub>2</sub>,  
 each R<sup>11F</sup> is independently lower alkyl, SR<sup>20F</sup>, OR<sup>20F</sup>, N(R<sup>6F</sup>)<sub>2</sub>, -COOR<sup>12F</sup>, -CON(R<sup>6F</sup>)<sub>2</sub>, -COR<sup>12F</sup>, CN, CF<sub>3</sub>, NO<sub>2</sub>  
 or halogen atom,

each R<sup>12F</sup> is independently hydrogen, lower alkyl or benzyl,

each R<sup>13F</sup> is independently hydrogen, halogen atom, lower alkyl, O-lower alkenyl, S-lower alkyl, N(R<sup>6F</sup>)<sub>2</sub>,  
 COOR<sup>12F</sup>, CN, CF<sub>3</sub> or NO<sub>2</sub>,

R<sup>14F</sup> and R<sup>15F</sup> are independently lower alkyl, halogen atom, CF<sub>3</sub>, OR<sup>16F</sup>, S(O)<sub>nF</sub>R<sup>16F</sup> or C(R<sup>16F</sup>)<sub>2</sub>OR<sup>17F</sup>,

each R<sup>16F</sup> is independently hydrogen, lower alkyl, lower alkenyl, Ph, Bn or CF<sub>3</sub>,

each R<sup>17F</sup> is independently hydrogen, lower alkyl or Bn,

each R<sup>18F</sup> is independently hydrogen, F or lower alkyl, or two R<sup>18F</sup> taken together, is 3-6 membered ring optionally  
 containing one heteroatom selected from oxygen, S(O)<sub>nF</sub> and nitrogen,

each R<sup>19F</sup> is independently lower alkyl, lower alkenyl, lower alkynyl, CF<sub>3</sub>, HET(R<sup>aF</sup>)<sub>4-9</sub>, lower alkyl-HET(R<sup>aF</sup>)<sub>4-9</sub>,  
 lower alkenyl-HET(R<sup>aF</sup>)<sub>4-9</sub>,

each R<sup>20F</sup> is independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, CF<sub>3</sub> or Ph(R<sup>13F</sup>)<sub>2</sub>,

each R<sup>aF</sup> is independently selected from the following group:

hydrogen, hydroxy, halogen atom, CN, NO<sub>2</sub>, amino, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkoxy, C2-6  
 alkenyloxy, C2-6 alkynyloxy, C1-6 alkylamino, di(C1-6 alkyl)amino, CF<sub>3</sub>, C(O)C1-6 alkyl, C(O)C2-6 alkenyl, C  
 (O)C2-6 alkynyl, COOH, COO(C1-6)alkyl, COO(C2-6)alkenyl and COO(C2-6)alkynyl, said alkyl, alkenyl, alky-  
 nyl, and alkyl portions of alkylamino and dialkylamino being optionally substituted by 1-3 of hydroxy, halogen  
 atom, aryl, C1-6 alkoxy, C2-6 alkenyloxy, C2-6 alkynyloxy, CF<sub>3</sub>, CO(C1-6)alkyl, CO(C2-6)alkenyl, CO(C2-6)  
 alkynyl, COOH, COO(C1-6)alkyl, COO(C2-6)alkenyl, COO(C2-6)alkynyl NH<sub>2</sub>, NH(C1-6)alkyl and N(C1-6)  
 alkyl)<sub>2</sub>; or a non-toxic salt thereof,

(7) in the specification of WO 2000/20371, the compound of formula (IG)



wherein Ar<sup>1G</sup> is aryl or heteroaryl, optionally substituted by R<sup>1G</sup> or R<sup>3G</sup>,

R<sup>1G</sup> is Y<sup>G</sup><sub>mG</sub>-R<sup>2G</sup>, Y<sup>G</sup><sub>mG</sub>-Ar<sup>3G</sup>, halogen atom, N(R<sup>5G</sup>)<sub>2</sub>, CN, NO<sub>2</sub>, C(R<sup>6G</sup>)<sub>3</sub>, CON(R<sup>5G</sup>)<sub>2</sub>, S(O)<sub>nG</sub>R<sup>7G</sup> or hydroxy,  
 Y<sup>G</sup> is a linker between R<sup>2G</sup> or Ar<sup>3G</sup> and Ar<sup>1G</sup> containing 0-4 carbon atoms and not more than one heteroatom  
 selected from oxygen, nitrogen and sulfur, said linker optionally containing CO, S(O)<sub>nG</sub>, -C=C- or acetylenic group,  
 and said linker being optionally substituted by R<sup>2G</sup>,

m<sup>G</sup> is 0 or 1,

n<sup>G</sup> is 0, 1 or 2,

R<sup>2G</sup> is hydrogen, F, CHF<sub>2</sub>, CF<sub>3</sub>, lower alkyl or hydroxy(C1-6)alkyl, or two R<sup>2G</sup> taken together, is carbocyclic ring  
 of up to six members, said ring containing not more than one heteroatom selected from oxygen, nitrogen or sulfur,  
 Ar<sup>3G</sup> is aryl or heteroaryl, optionally substituted by R<sup>3G</sup>,

R<sup>3G</sup> is R<sup>4G</sup>, halogen atom, halo(C1-6)alkyl, N(R<sup>5G</sup>)<sub>2</sub>, CN, NO<sub>2</sub>, C(R<sup>6G</sup>)<sub>3</sub>, CON(R<sup>5G</sup>)<sub>2</sub>, OR<sup>4G</sup>, SR<sup>4G</sup> or S(O)<sub>nG</sub>R<sup>7G</sup>,

R<sup>4G</sup> is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, CHF<sub>2</sub> or CF<sub>3</sub>,

R<sup>5G</sup> is R<sup>4G</sup>, Ph or Bn, or two R<sup>5G</sup> taken together, is a ring of up to six members containing carbon atoms and 0-2  
 heteroatoms selected from oxygen, nitrogen or sulfur,

R<sup>6G</sup> is hydrogen, F, CF<sub>3</sub> or lower alkyl, or two R<sup>6G</sup> taken together, is a ring of up to six members containing carbon  
 atoms and 0-2 heteroatoms selected from oxygen, nitrogen or sulfur,

R<sup>7G</sup> is lower alkyl, lower alkenyl, lower alkynyl, CHF<sub>2</sub>, CF<sub>3</sub>, N(R<sup>5G</sup>)<sub>2</sub>, Ph(R<sup>8G</sup>)<sub>2</sub> or CH<sub>2</sub>Ph(R<sup>8G</sup>)<sub>2</sub>,

R<sup>8G</sup> is R<sup>4G</sup>, OR<sup>4G</sup> SR<sup>4G</sup> or halogen atom,

W<sup>G</sup> is a 3-6 membered linking group containing 0-2 heteroatoms selected from oxygen, nitrogen and sulfur, said  
 linking group optionally containing CO, S(O)<sub>mG</sub>, C=C, acetylenic group, and optionally being substituted by R<sup>9G</sup>,

R<sup>9G</sup> is R<sup>2G</sup>, lower alkyl, lower alkynyl, OR<sup>4G</sup> or SR<sup>4G</sup>,

Ar<sup>2G</sup> is aryl or heteroaryl, optionally substituted by R<sup>3G</sup>,

R<sup>10G</sup> is R<sup>4G</sup>, halogen atom, N(R<sup>5G</sup>)<sub>2</sub>, CN, NO<sub>2</sub>, C(R<sup>6G</sup>)<sub>3</sub>, OR<sup>4G</sup>, SR<sup>4G</sup> or S(O)<sub>nG</sub>R<sup>7G</sup>,

X<sup>G</sup> is a linker which is attached to Ar<sup>2G</sup> ortho to the attachment of W<sup>G</sup>, said linker containing 0-4 carbon atoms  
 and not more than one heteroatom selected from oxygen, nitrogen and sulfur, said linker further optionally con-  
 taining CO, S(O)<sub>mG</sub>, C=C or acetylenic group, and said linker being optionally substituted by R<sup>11G</sup>,

R<sup>11G</sup> is R<sup>9G</sup>,



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$Q^G$  is a member selected from the group consisting of  $COOH$ , tetrazole,  $SO_3H$ , hydroxamic acid,  $CONHSO_2R^{12G}$  and  $SO_2NHCOR^{12G}$ ,

$R^{12G}$  is a member selected from the group consisting of  $CF_3$ , lower alkyl, lower alkenyl, lower alkynyl and  $Z^GA^4G$ ,

$Z^G$  is a linker containing 0-4 carbon atom, optionally substituted by  $R^{13G}$ ,

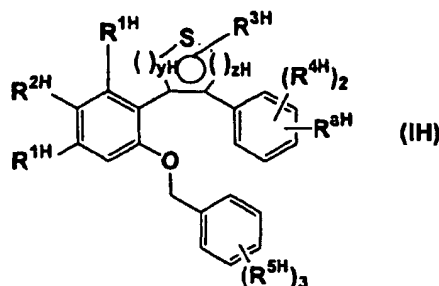
$R^{13G}$  is  $R^{9G}$ ,

$A^4G$  is aryl or heteroaryl, optionally substituted by  $R^{14G}$ ,

$R^{14G}$  is  $R^{10G}$  or  $NHCOMe$ ;

or an non-toxic salt thereof;

(8) in the specification of WO 2001/19814, the compound of formula (IH)



wherein  $y^H$  and  $z^H$  are independently 0-2, with the proviso that  $y^H + z^H = 2$ ,  
 $R^{aH}$  is

1) heteroaryl, wherein heteroaryl is selected from the group (a) - (n):

(a) fury, (b) diaziny, triaziny or tetraziny, (c) imidazolyl, (d) isoxazolyl, (e) isothiazolyl, (f) oxadiazolyl, (g) oxazolyl, (h) pyrazolyl, (i) pyrrolyl, (j) thiadiazolyl, (k) thiazolyl, (l) thienyl, (m) triazolyl and (n) tetrazolyl, wherein heteroaryl is optionally substituted by one or more substituents independently selected from  $R^{11H}$  and C1-4 alkyl;

2)  $-COR^{6H}$ ,

3)  $-NR^{7H}R^{8H}$ ,

4)  $-SO_2R^{9H}$ ,

5) hydroxy,

6) C1-6 alkoxy, optionally substituted by one or more substituents independently selected from  $R^{11H}$ , and

7) C1-6 alkyl, C2-6 alkenyl or C3-6 cycloalkyl, optionally substituted by one or more substituents independently selected from  $R^{11H}$ , and further substituted by 1-3 substituents independently selected from the group of (a) - (h):

(a)  $-COR^{6H}$ , (b)  $-NR^{7H}R^{8H}$ , (c)  $-SO_2R^{9H}$ , (d) hydroxy, (e) C1-6 alkoxy or haloC1-6 alkoxy, and (f) heteroaryl;

$R^{aH}$  is positioned on the phenyl ring to which it is bonded in a 1, 3 or 1, 4 relationship relative to the thienyl group of formula (IH),

$R^{1H}$ ,  $R^{2H}$ ,  $R^{3H}$ ,  $R^{4H}$  and  $R^{5H}$  are independently selected from the following group:

1) hydroxy, 2) halogen atom, 3) C1-6 alkyl, 4) C1-6 alkoxy, 5) C1-6 alkylthio, 6) nitro, 7) carboxy, and 8) CN, wherein groups of 3) — 5) are optionally substituted by one or more substituents independently selected from  $R^{11H}$ ,

$R^{6H}$  is hydrogen, hydroxy, C1-6 alkyl, C1-6 alkoxy and  $NR^{7H}R^{8H}$ , wherein C1-6 alkyl and C1-6 alkoxy are optionally substituted by one or more substituents independently selected from  $R^{11H}$ ,

$R^{7H}$  and  $R^{8H}$  are independently selected from the group: 1) hydrogen, 2) hydroxy, 3)  $SO_2R^{9H}$ , 4) C1-6 alkyl, 5) C1-6 alkoxy, 6) phenyl, 7) naphthyl, 8) furyl, 9) thienyl and 10) pyridyl, wherein groups of 4) — 5) are optionally substituted by one or more substituents independently selected from  $R^{11H}$ , and groups of 6) — 10)

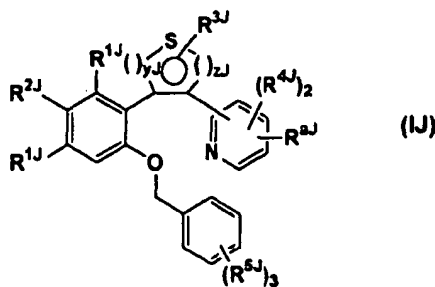
are optionally substituted by one or more substituents independently selected from  $R^{11H}$  or C1-4 alkyl,  $R^{9H}$  is selected from the group:

1) hydroxy, 2)  $N(R^{10H})_2$ , 3) C1-6 alkyl, optionally substituted by one or more substituents independently selected from  $R^{11H}$ , 4) phenyl, 5) naphthyl, 6) furyl, 7) thienyl, and 8) pyridyl, groups of 4) — 8) are optionally substituted by one or more substituents independently selected from  $R^{11H}$  and C1-4 alkyl,

$R^{10H}$  is hydrogen or C1-6 alkyl,

$R^{11H}$  is halogen atom, hydroxy, C1-3 alkoxy, nitro,  $N(R^{10H})_2$ , and pyridyl; or a pharmaceutically acceptable salt, hydrate or ester thereof,

(9) in the specification of WO 2001/19819, the compound of formula (IJ)



wherein  $y^J$  and  $z^J$  are independently 0-2, with the proviso that  $y^J + z^J = 2$ ,  $R^{6J}$  is

1) heteroaryl, wherein heteroaryl is selected from the group (a) - (n):

(a) fury, (b) diaziny, triaziny or tetraziny, (c) imidazolyl, (d) isoxazolyl, (e) isothiazolyl, (f) oxadiazolyl, (g) oxazolyl, (h) pyrazolyl, (i) pyrrolyl, (j) thiadiazolyl, (k) thiazolyl, (l) thienyl, (m) triazolyl and (n) tetrazolyl, wherein heteroaryl is optionally substituted by one or more substituents independently selected from  $R^{11J}$  and C1-4 alkyl;

2)  $—COR^{6J}$ ,

3)  $—NR^{7J}R^{8J}$ ,

4)  $—SO_2R^{9J}$ ,

5) hydroxy,

6) C1-6 alkoxy, optionally substituted by one or more substituents independently selected from  $R^{11J}$ , and

7) C1-6 alkyl, C2-6 alkenyl or C3-6 cycloalkyl, optionally substituted by one or more substituents independently selected from  $R^{11H}$ , and further substituted by 1-3 substituents independently selected from the group of (a) - (f):

(a)  $—COR^{6J}$ , (b)  $—NR^{7J}R^{8J}$ , (c)  $—SO_2R^{9J}$ , (d) hydroxy, (e) C1-6 alkoxy or haloC1-6 alkoxy, and (f) heteroaryl,

$R^{6J}$  is positioned on the pyridyl ring to which it is bonded in a 1, 3 or 1, 4 relationship relative to the thienyl group of formula (IJ),

$R^{1J}$ ,  $R^{2J}$ ,  $R^{3J}$ ,  $R^{4J}$  and  $R^{5J}$  are independently selected from the following group:

1) hydroxy, 2) halogen atom, 3) C1-6 alkyl, 4) C1-6 alkoxy, 5) C1-6 alkylthio, 6) nitro, 7) carboxy, and 8) CN, wherein groups of 3) — 5) are optionally substituted by one or more substituents independently selected from  $R^{11J}$ ,

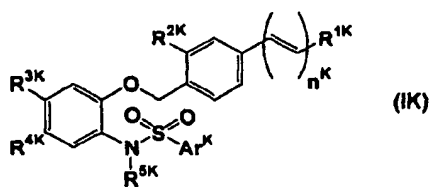
$R^{6J}$  is hydrogen, hydroxy, C1-6 alkyl, C1-6 alkoxy and  $NR^{7J}R^{8J}$ , wherein C1-6 alkyl and C1-6 alkoxy are optionally substituted by one or more substituents independently selected from  $R^{11J}$ ,

$R^{7J}$  and  $R^{8J}$  are independently selected from the group: 1) hydrogen, 2) hydroxy, 3)  $SO_2R^{9J}$  4) C1-6 alkyl, 5) C1-6 alkoxy, 6) phenyl, 7) naphthyl, 8) furyl, 9) thienyl and 10) pyridyl, wherein groups of 4) — 5) are optionally

substituted by one or more substituents independently selected from  $R^{11J}$ , and groups of 6) — 10) are optionally substituted by one or more substituents independently selected from  $R^{11J}$  or C1-4 alkyl,  $R^{9J}$  is selected from the group:

- 1) hydroxy, 2)  $N(R^{10J})_2$ , 3) C1-6 alkyl, optionally substituted by one or more substituents independently selected from  $R^{11J}$ , 4) phenyl, 5) naphthyl, 6) furyl, 7) thienyl, and 8) pyridyl, groups of 4) — 8) are optionally substituted by one or more substituents independently selected from  $R^{11J}$  and C1-4 alkyl,  $R^{10J}$  is hydrogen or C1-6 alkyl,  $R^{11J}$  is halogen atom, hydroxy, C1-3 alkoxy, nitro,  $N(R^{10J})_2$ , and pyridyl; or a pharmaceutically acceptable salt, hydrate or ester thereof;

(10) N-phenyl-aryl-sulfonamide compound of formula (IK)



wherein  $R^{1K}$  is  $COOH$ , hydroxymethyl, 5-tetrazolyl, 5-oxo-1,2,4-oxadiazolyl or 5-oxo-1,2,4-thiadiazolyl,

$R^{2K}$  is hydrogen, methyl, methoxy or chloro,

$R^{3K}$  and  $R^{4K}$  are a combination of (1) methyl and methyl, (2) methyl and chloro, (3) chloro and methyl, or (4) trifluoromethyl and hydrogen; or  $R^3$  and  $R^4$  are taken together with the carbon to which  $R^3$  and  $R^4$  are attached to form (5) cyclopentene, (6) cyclohexene or (7) benzene ring,

$R^{5K}$  is isopropyl, isobutyl, 2-methyl-2-propenyl, cyclopropylmethyl, methyl, ethyl, propyl, 2-propenyl or 2-hydroxy-2-methylpropyl,

$Ar^K$  is thiazolyl optionally substituted with methyl, pyridyl or 5-methyl-2-furyl,

$n^K$  is 0 or 1, with the proviso that when  $R^{1K}$  is 5-tetrazolyl, 5-oxo-1,2,4-oxadiazolyl or 5-oxo-1,2,4-thiadiazolyl, and then  $n$  is 0,

an alkyl ester thereof or a non-toxic salt thereof.

[0015] The above compound of formula (IA) — (IK) may be converted into a corresponding pharmaceutically acceptable salt by known methods. Non-toxic salts and watersoluble salts are preferred.

[0016] Appropriate salts are salts of alkali metals (e.g. potassium, sodium), salts of alkaline-earth metals (e.g. calcium, magnesium), ammonium salts (e.g. tetramethylammonium), salts of pharmaceutically acceptable organic amines (e.g. triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)methylamine, lysine, arginine, N-methyl-D-glucamine).

[0017] Non-toxic and watersoluble acid addition salts are preferable. Appropriate acid addition salts are, salts of inorganic acids, such as hydrochloride, hydrobromide, sulfate, phosphate, nitrate; salts of organic acid, such as acetate, trifluoroacetate, lactate, tartrate, oxalate, fumarate, maleate, citrate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, toluenesulphonate, isethionate, glucuronate, gluconate.

[0018] The compound of the present invention and a non-toxic salt thereof may be converted into the corresponding a hydrate thereof by conventional means.

[0019] The compound of the present invention, a non-toxic salt thereof or a hydrate thereof may be converted into the corresponding a cyclodextrin clathrate thereof by conventional means.

[0020] As the concretely compound of formula (IA) — (IJ) in the present invention, compounds described in the specification in WO 98/27053, EP 878465, WO 92/19617, WO 96/06822, WO 97/00863, WO 99/47497, WO 00/20371, WO 2001/19814, WO 2001/19819, for example, compounds described in Examples are preferable.

[0021] As the concretely compound of formula (IK), the compound described in Examples of this specification are preferable.

[0022] In the compounds described in the above specification, compounds which bond to  $EP_1$  receptor and show an antagonistic action are preferable. More preferably, compounds which specifically bond to  $EP_1$  receptor and show an antagonistic action.

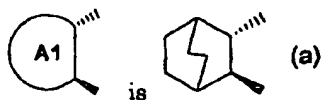
[0023] The compound of formula (IA) — (IK) may be prepared by method described in each corresponding published International application, published European patent application or the specification of Japanese application.

[0024] In the present invention,  $EP_1$  antagonists are not limited in order to achieve the object that is treatment and/

or prevention depression. Especially, following compounds are preferable.

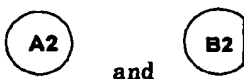
[0025] In the compound of formula (IA) — (IK), the compound of formula (IA), (IB) and (IK) are preferable.

1) In the compound of formula (IA), the compound in which



is preferable.

2) In the compound of formula (IB), the compound in which



are C5-15 carbocyclic ring,

Z<sup>5</sup> is 5-7 membered heterocyclic ring containing 1 or 2 oxygens, sulfurs or nitrogens, which ring may be substituted by 1-5 of R<sup>5B</sup> in which multiple R<sup>5B</sup> each, independently, is hydrogen, C1-6 alkyl, C1-6 alkoxy, C1-6 alkylthio, nitro, halogen atom, trifluoromethyl, trifluoromethoxy or hydroxy;

is preferable.

3) In the compound of formula (IK), all compounds are preferable, especially, the compound in which Ar<sup>k</sup> is 5-methyl-2-furyl, 2-thiazolyl, 5-methyl-2-thiazolyl, 2-pyridyl, 3-pyridyl is preferable. Concretely, following compounds are preferable.

- (1) 4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl]cinnamic acid,
- (2) 4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl]benzoic acid,
- (3) 4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl]benzoic acid,
- (4) 4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4-chloro-5-methylphenoxy]methyl]benzoic acid,
- (5) 4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]benzoic acid,
- (6) 4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]benzoic acid,
- (7) 3-methyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4-methyl-5-chlorophenoxy]methyl]benzoic acid,
- (8) 3-methyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4-chloro-5-methylphenoxy]methyl]benzoic acid,
- (9) 3-chloro-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4-methyl-5-chlorophenoxy]methyl]benzoic acid,
- (10) 3-chloro-4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-4-methyl-5-chlorophenoxy]methyl]benzoic acid,
- (11) 3-methoxy-4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-4-methyl-5-chlorophenoxy]methyl]benzoic acid,
- (12) 3-methyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]benzoic acid,
- (13) 3-methoxy-4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]benzoic acid,
- (14) 3-methoxy-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]benzoic acid,
- (15) 3-methoxy-4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-4-chloro-5-methylphenoxy]methyl]benzoic acid,
- (16) 3-chloro-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]benzoic acid,
- (17) 3-chloro-4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]benzoic acid,
- (18) 3-methyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4-chloro-5-methylphenoxy]methyl]cinnamic acid,
- (19) 4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-4-methyl-5-chlorophenoxy]methyl]cinnamic acid,
- (20) 4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4-methyl-5-chlorophenoxy]methyl]cinnamic acid,
- (21) 4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]cinnamic acid,
- (22) 3-methyl-4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl]cinnamic acid,
- (23) 3-methyl-4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]benzoic acid,

- (24) 3-methyl-4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]cinnamic acid,  
 (25) 3-methyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]cinnamic acid,  
 (26) 4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4, 5-dimethyl phenoxy]methyl]cinnamic acid,  
 (27) N-[4-chloro-5-methyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide,  
 (28) 3-methoxy-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4-methyl-5-chlorophenoxy]methyl]cinnamic acid,  
 (29) N-[4, 5-dimethyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide,  
 (30) N-[4, 5-dimethyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-(5-methyl-2-furyl)sulfonylamide,  
 (31) N-[4-chloro-5-methyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide,  
 (32) N-[4-chloro-5-methyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isopropyl-(5-methyl-2-furyl)sulfonylamide,  
 (33) N-[4-chloro-5-methyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide,  
 (34) 4-[6-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl]benzoic acid,  
 (35) 4-[6-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl]benzoic acid,  
 (36) 4-[7-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-1,2,3,4-tetrahydronaphthalen-6-yloxy]methyl]benzoic acid,  
 (37) 4-[7-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-1,2,3,4-tetrahydronaphthalen-6-yloxy]methyl]benzoic acid,  
 (38) N-(4, 5-dimethyl-2-[2-methyl-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy] phenyl)-N-isopropyl-(5-methyl-2-furyl)sulfonylamide,  
 (39) N-[4, 5-dimethyl-2-[2-methyl-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy] phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide,  
 (40) N-[4, 5-dimethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-(5-methyl-2-furyl)sulfonylamide,  
 (41) N-[4, 5-dimethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide,  
 (42) N-(4, 5-dimethyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl)-N-isobutyl-(5-methyl-2-furyl)sulfonylamide,  
 (43) 3-methyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4-methyl-5-chlorophenoxy]methyl]cinnamic acid,  
 (44) N-[4, 5-dimethyl-2-[2-methoxy-4-(5-oxo-1,2,4-oxadiazol-3-yl) phenylmethoxy]phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide,  
 (45) N-[4,5-dimethyl-2-[2-methoxy-4-(5-oxo-1,2,4-oxadiazol-3-yl) phenylmethoxy]phenyl]-N-isopropyl-(5-methyl-2-furyl)sulfonylamide,  
 (46) 4-[6-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl] cinnamic acid,  
 (47) 3-methyl-4-[6-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl]benzoic acid,  
 (48) 3-methyl-4-[6-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid,  
 (49) 4-[2-[N-(2-methyl-2-propenyl)-N-(5-methyl-2-furylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]benzoic acid,  
 (50) 3-methyl-4-[6-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl]benzoic acid,  
 (51) 3-methyl-4-[6-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid,  
 (52) 4-[6-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid,  
 (53) 4-[3-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-2-naphthyloxy]methyl] benzoic acid,  
 (54) 3,5-dimethyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl]benzoic acid,  
 (55) 3-methyl-4-[6-[N-(2-methyl-2-propenyl)-N-(5-methyl-2-furylsulfonyl)amino] indan-5-yloxy]methyl]benzoic acid,  
 (56) 4-[6-[N-cyclopropylmethyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl]-3-methylbenzoic acid,  
 (57) 4-[6-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl]-3-methylbenzylalcohol,  
 (58) 3-methyl-4-[6-[N-methyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl]benzoic acid,  
 (59) 4-[6-[N-ethyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl]-3-methylbenzoic acid,  
 (60) 4-[6-[N-methyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid,  
 (61) 4-[6-[N-ethyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid,  
 (62) 4-[6-[N-propyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid,  
 (63) 4-[4, 5-dimethyl-2-[N-(2-methyl-2-propenyl)-N-(5-methyl-2-furylsulfonyl)amino]phenoxy]methyl]-3-methylbenzoic acid,  
 (64) 4-[6-[N-(2-methyl-2-propenyl)-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid,

- (65) 4-[6-[N-cyclopropylmethyl-N-(5-methyl-2-furylsulfonyl)aminolindan-5-yloxy)methyl]cinnamic acid,  
 (66) 4-[6-[N-(2-propenyl)-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy)methyl]cinnamic acid,  
 (67) 3-methyl-4-[6-[N-propyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy)methyl]benzoic acid,  
 (68) 3-methyl-4-[6-[N-(2-propenyl)-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy)methyl]benzoic acid,  
 5 (69) 4-[4,5-dimethyl-2-[N-methyl-N-(5-methyl-2-furylsulfonyl)amino]phenoxy methyl]benzoic acid,  
 (70) 4-[4, 5-dimethyl-2-[N-ethyl-N-(5-methyl-2-furylsulfonyl)amino]phenoxy methyl]benzoic acid,  
 (71) 4-[4, 5-dimethyl-2-[N-(5-methyl-2-furylsulfonyl)-N-propylamino]phenoxy methyl]benzoic acid,  
 (72) 4-[3-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]naphtharen-2-yloxy)methyl]-3-methylbenzoic acid,  
 (73) 4-[3-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]naphtharen-2-yloxy)methyl]-3-methylbenzoic acid,  
 10 (74) 4-[3-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]naphtharen-2-yloxy)methyl]cinnamic acid,  
 (75) 4-[3-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]naphtharen-2-yloxy)methyl]cinnamic acid,  
 (76) 3-methyl-4-[3-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]naphtharen-2-yloxy)methyl]cinnamic acid,  
 (77) 3-methyl-4-[3-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)aminonaphtharen-2-yloxy)methyl]cinnamic acid,  
 (78) 4-[4, 5-dimethyl-2-[N-[(5-methyl-2-furyl)sulfonyl]-N-2-propenylamino] phenoxy)methyl]benzoic acid,  
 15 (79) 4-[4, 5-dimethyl-2-(N-methyl-N-(5-methyl-2-furylsulfonyl)amino] phenoxy)methyl]-3-methylbenzoic acid,  
 (80) 4-[4, 5-dimethyl-2-[N-ethyl-N-(5-methyl-2-furylsulfonyl)amino]phenoxy)methyl]-3-methylbenzoic acid,  
 (81) 4-[4, 5-dimethyl-2-[N-(5-methyl-2-furylsulfonyl)-N-propylamino]phenoxy)methyl]-3-methylbenzoic acid,  
 (82) 4-[4,5-dimethyl-2-[N-(5-methyl-2-furylsulfonyl)-N-(2-propenyl)amino] phenoxy)methyl]-3-methylbenzoic acid,  
 (83) 4-[4, 5-dimethyl-2-[N-(2-hydroxy-2-methylpropyl)-N-(5-methyl-2-furylsulfonyl) amino]phenoxy)methyl]-  
 20 3-methylbenzoic acid,  
 (84) 4-[6-[N-(2-hydroxy-2-methylpropyl)-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy)methyl]-3-methylbenzoic acid,  
 (85) 4-[4, 5-dimethyl-2-[N-cyclopropylmethyl-N-(5-methyl-2-furylsulfonyl) amino]phenoxy)methyl]benzoic acid,  
 (86) 4-[4, 5-dimethyl-2-[N-(2-hydroxy-2-methylpropyl)-N-(5-methyl-2-furylsulfonyl) amino]phenoxy)methyl]benzoic  
 25 acid,  
 (87) 4-[6-[N-(2-hydroxy-2-methylpropyl)-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy)methyl]cinnamic acid,  
 (88) 4-[4, 5-dimethyl-2-[N-cyclopropylmethyl-N-(5-methyl-2-furylsulfonyl)amino] phenoxy)methyl]-3-methylbenzoic acid.  
 (89) 4-[2-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy)methyl] benzoic acid,  
 30 (90) 4-[2-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy)methyl] benzoic acid,  
 (91) 4-[2-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy)methyl] cinnamic acid,  
 (92) 4-[2-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy)methyl] cinnamic acid,  
 (93) 4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy)methyl]benzoic acid,  
 (94) 4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy)methyl]cinnamic acid,  
 35 (95) 4-[2-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]-4-chloro-5-methylphenoxy methyl]benzoic acid,  
 (96) N-[4-trifluoromethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-2-thiazolylsulfonylamide,  
 (97) N-[4-trifluoromethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-2-thiazolylsulfonylamide,  
 (98) N-[4-trifluoromethyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isopropyl-2-thiazolylsulfo-  
 40 nylamide,  
 (99) N-[4-trifluoromethyl-2-[4-(5-oxo-1,2,4-thiadiazol-3-yl)phenylmethoxy]phenyl]-N-isopropyl-2-thiazolylsulfo-  
 nylamide,  
 (100) 4-[2-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-chloro-5-methylphenoxy)methyl]benzoic acid,  
 (101) 4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-chloro-5-methylphenoxy)methyl]benzoic acid,  
 (102) 3-chloro-4-[2-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-chloro-5-methylphenoxy)methyl]benzo-  
 45 ic acid,  
 (103) 3-methyl-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy)methyl]benzoic acid,  
 (104) 3-methyl-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-chloro-5-methylphenoxy)methyl]benzoic acid,  
 50 (105) 3-methoxy-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-chloro-5-methylphenoxy)methyl]benzoic acid,  
 (106) 3-methoxy-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy)methyl]benzoic acid,  
 (107) N-[4-trifluoromethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonyla-  
 55 mide,  
 (108) N-[4-trifluoromethyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide,  
 (109) N-[4-trifluoromethyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isobutyl-(4-methyl-2-thia-

zoly)sulfonylamide,

(110) 4-[2-(N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino)-4-methyl-5-chlorophenoxymethyl]benzoic acid,

(111) 3-chloro-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-methyl-5-chlorophenoxymethyl]benzoic acid,

(112) 3-methoxy-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-methyl-5-chlorophenoxymethyl]benzoic acid,

(113) N-[4-(4-trifluoromethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl)-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide,

(114) 3-methyl-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxymethyl]benzoic acid,

(115) 3-methyl-4-[2-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxymethyl]benzoic acid,

(116) 3-methoxy-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxymethyl]benzoic acid,

(117) 3-chloro-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxymethyl]benzoic acid,

(118) 3-chloro-4-[2-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxymethyl]benzoic acid,

(119) 4-[2-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxymethyl]benzoic acid,

(120) 4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxymethyl]benzoic acid,

(121) 4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-chloro-5-methylphenoxymethyl]cinnamic acid,

(122) 3-methyl-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxymethyl]cinnamic acid,

(123) 3-chloro-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxymethyl]cinnamic acid,

(124) 3-methyl-4-[2-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxymethyl]cinnamic acid,

(125) 3-methyl-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxymethyl]cinnamic acid,

(126) 4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-methyl-5-chlorophenoxymethyl]cinnamic acid,

(127) 3-methyl-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-methyl-5-chlorophenoxymethyl]cinnamic acid,

(128) 3-methyl-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-chloro-5-methylphenoxymethyl]cinnamic acid,

(129) N-[4-chloro-5-methyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide,

(130) N-[4-chloro-5-methyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide,

(131) 4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxymethyl]cinnamic acid,

(132) N-[4-(4-trifluoromethyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl)-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide,

(133) N-[4-(4-trifluoromethyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl)-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide,

(134) 3-chloro-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxymethyl]cinnamic acid,

(135) N-[4, 5-dimethyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide,

(136) N-[4, 5-dimethyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide,

(137) N-[4, 5-dimethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide,

(138) N-[4, 5-dimethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide,

(139) N-[4-chloro-5-methyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide,

(140) N-[4-chloro-5-methyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide,

(141) N-[4-chloro-5-methyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide,

(142) N-[4-chloro-5-methyl-2-[2-methyl-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide,

- (143) 3-methoxy-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]cinnamic acid,  
 (144) N-[4, 5-dimethyl-2-[2-methyl-4-(5-oxo-1,2,4-oxadiazol-3-yl)]phenyl methyloxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide,  
 5 (145) N-[4,5-dimethyl-2-[2-methyl-4-(5-oxo-1,2,4-oxadiazol-3-yl)]phenylmethyloxy] phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide,  
 (146) N-[4, 5-dimethyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)]phenylmethyloxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide,  
 10 (147) N-(4,5-dimethyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)]phenylmethyloxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide,  
 (148) N-[4, 5-dimethyl-2-[2-methoxy-4-(5-oxo-1,2,4-oxadiazol-3-yl)]phenylmethyloxy] phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide,  
 (149) N-[4, 5-dimethyl-2-[2-methoxy-4-(5-tetrazolyl)]phenylmethyloxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide,  
 15 (150) 4-[6-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]benzoic acid,  
 (151) 4-[6-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid,  
 (152) 3-methyl-4-[6-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]benzoic acid,  
 (153) 3-methyl-4-[6-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid,  
 20 (154) 3-methyl-4-[2-[N-(2-methyl-2-propenyl)-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-chloro-5-methylphenoxy]methyl]benzoic acid,  
 (155) 4-[2-[N-(2-methyl-2-propenyl)-N-(4-methyl-2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl]cinnamic acid,  
 (156) 3-methyl-4-[2-[N-(2-methyl-2-propenyl)-N-(4-methyl-2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]benzoic acid,  
 25 (157) 3-methyl-4-[6-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]benzoic acid,  
 (158) 3-methyl-4-[6-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]benzoic acid,  
 (159) 3-methyl-4-[6-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]benzoic acid,  
 (160) 4-[6-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]benzoic acid,  
 30 (161) 4-[6-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]benzoic acid,  
 (162) 4-[6-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]benzoic acid,  
 (163) 4-[6-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid,  
 (164) 3-methyl-4-[6-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid,  
 (165) 4-[2-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl] benzoic acid,  
 35 (166) 4-[2-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl] benzoic acid,  
 (167) 4-[2-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl] cinnamic acid,  
 (168) 4-[2-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl] cinnamic acid,  
 (169) 4-[6-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid,  
 (170) 4-[6-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid,  
 40 (171) 3-methyl-4-[2-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]benzoic acid,  
 (172) 3-methyl-4-[2-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]benzoic acid,  
 (173) 3-methyl-4-[2-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]cinnamic acid,  
 (174) 3-methyl-4-[2-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]cinnamic acid,  
 (175) 3-methyl-4-[6-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid,  
 45 (176) 3-methyl-4-[6-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid,  
 (177) 4-[3-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]naphtharen-2-yloxy]methyl]benzoic acid,  
 (178) 4-[3-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]naphtharen-2-yloxy]methyl]benzoic acid,  
 (179) 4-[3-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]naphtharen-2-yloxy]methyl]-3-methylbenzoic acid,  
 50 (180) 4-[3-[N-isopropyl-N-[2-(4-methylthiazolyl)sulfonyl]amino]naphtharen-2-yloxy]methyl]-3-methylbenzoic acid,  
 (181) 4-[3-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]naphtharen-2-yloxy]methyl]cinnamic acid,  
 (182) 4-[3-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]naphtharen-2-yloxy]methyl]cinnamic acid,  
 (183) 4-[4, 5-dimethyl-2-(N-methyl-N-(4-methyl-2-thiazolylsulfonyl)amino] phenoxy]methyl]-3-methylbenzoic acid,  
 (184) 4-[4, 5-dimethyl-2-[N-ethyl-N-(4-methyl-2-thiazolylsulfonyl)amino] phenoxy]methyl]-3-methylbenzoic acid,  
 55 (185) 4-[4, 5-dimethyl-2-(N-propyl-N-(4-methyl-2-thiazolylsulfonyl)amino] phenoxy]methyl]-3-methylbenzoic acid,  
 (186) 4-[4, 5-dimethyl-2-[N-(2-propenyl)-N-(4-methyl-2-thiazolylsulfonyl)amino] phenoxy]methyl]-3-methylbenzoic acid,  
 (187) 4-[4, 5-dimethyl-2-(N-cyclopropylmethyl-N-(4-methyl-2-thiazolylsulfonyl)amino] phenoxy]methyl]-3-methylbenzoic acid,  
 (188) 4-[4, 5-dimethyl-2-[N-(2-hydroxy-2-methylpropyl)-N-(4-methyl-2-thiazolyl sulfonyl)amino]phenoxy]methyl]-



- 3-methylbenzoic acid,  
 (189) 4-[6-[N-(2-methyl-2-propenyl)-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]benzoic acid,  
 (190) 4-[6-[N-(4-methyl-2-thiazolylsulfonyl)-N-(2-propenyl)amino]indan-5-yloxymethyl]benzoic acid,  
 (191) 4-[6-[N-cyclopropylmethyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]benzoic acid,  
 5 (192) 4-[3-[N-isobutyl-N-[2-(4-methylthiazolyl)sulfonyl]amino]naphtharene-2-yloxymethyl]benzoic acid,  
 (193) 4-[3-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]naphtharene-2-yloxymethyl]-3-methylbenzoic acid,  
 (194) 4-[6-[N-ethyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]benzoic acid,  
 (195) 4-[6-[N-(4-methyl-2-thiazolylsulfonyl)-N-propylamino]indan-5-yloxymethyl]benzoic acid,  
 (196) 4-[6-[N-methyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]benzoic acid,  
 10 (197) 3-methyl-4-[6-[N-methyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]cinnamic acid,  
 (198) 4-[6-[N-ethyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]-3-methylcinnamic acid,  
 (199) 3-methyl-4-[6-[N-(2-methyl-2-propenyl)-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]cinnamic acid,  
 (200) 4-[6-[N-cyclopropylmethyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]-3-methylcinnamic acid,  
 15 (201) 3-methyl-4-[6-[N-(4-methyl-2-thiazolylsulfonyl)-N-(2-propenyl)amino]indan-5-yloxymethyl]cinnamic acid,  
 (202) 4-[6-[N-(2-hydroxy-2-methylpropyl)-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]-3-methylcinnamic acid,  
 (203) 3-methyl-4-[6-[N-(4-methyl-2-thiazolylsulfonyl)-N-propylamino]indan-5-yloxymethyl]cinnamic acid,  
 20 (204) 4-[6-[N-(2-hydroxy-2-methylpropyl)-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]benzoic acid,  
 (205) 4-[2-[N-isobutyl-N-(2-pyridylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl]cinnamic acid,  
 (206) 4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl]benzoic acid,  
 (207) 3-chloro-4-[2-[N-isopropyl-N-(2-pyridylsulfonyl)amino]-4-chloro-5-methylphenoxy]methyl]benzoic acid,  
 25 (208) 3-methyl-4-[2-[N-isobutyl-N-(2-pyridylsulfonyl)amino]-4-chloro-5-methylphenoxy]methyl]benzoic acid,  
 (209) 3-methyl-4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4-chloro-5-methylphenoxy]methyl]benzoic acid,  
 (210) 3-methyl-4-[2-[N-isobutyl-N-(2-pyridylsulfonyl)amino]-4-methyl-5-chlorophenoxy]methyl]benzoic acid,  
 (211) N-[4-trifluoromethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-3-pyridylsulfonylamide,  
 (212) N-[4-trifluoromethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-3-pyridylsulfonylamide,  
 30 (213) 4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4-methyl-5-chlorophenoxy]methyl]benzoic acid,  
 (214) 3-chloro-4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4-methyl-5-chlorophenoxy]methyl]benzoic acid,  
 (215) 3-methyl-4-[2-[N-isobutyl-N-(2-pyridylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl]cinnamic acid,  
 (216) 3-methoxy-4-[2-[N-isobutyl-N-(2-pyridylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]benzoic acid,  
 (217) 3-methoxy-4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]benzoic acid,  
 35 (218) 3-methyl-4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]benzoic acid,  
 (219) 3-methyl-4-[2-[N-isobutyl-N-(2-pyridylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]benzoic acid,  
 (220) N-[4-trifluoromethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-2-pyridylsulfonylamide,  
 (221) N-[4-trifluoromethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-2-pyridylsulfonylamide,  
 (222) 3-methyl-4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4-methyl-5-chlorophenoxy]methyl]benzoic acid,  
 40 (223) 4-[2-[N-isobutyl-N-(2-pyridylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]benzoic acid,  
 (224) N-[4-trifluoromethyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isobutyl-2-pyridylsulfonylamide,  
 (225) 4-[2-[N-isopropyl-N-(2-pyridylsulfonyl)amino]-4-methyl-5-chlorophenoxy]methyl]cinnamic acid,  
 (226) 3-methyl-4-[2-[N-isobutyl-N-(2-pyridylsulfonyl)amino]-4-methyl-5-chlorophenoxy]methyl]cinnamic acid,  
 45 (227) 3-methyl-4-[2-[N-isobutyl-N-(2-pyridylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]cinnamic acid,  
 (228) 4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]cinnamic acid,  
 (229) 3-methyl-4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]cinnamic acid,  
 (230) N-[4-trifluoromethyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-2-pyridylsulfonylamide,  
 50 (231) 3-chloro-4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]cinnamic acid,  
 (232) N-[4, 5-dimethyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-2-pyridylsulfonylamide,  
 (233) N-[4, 5-dimethyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-3-pyridylsulfonylamide,  
 (234) N-[4-chloro-5-methyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-3-pyridylsulfonylamide,  
 (235) N-[4, 5-dimethyl-2-[2-chloro-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-2-pyridylsulfonylamide,  
 55 (236) N-[4, 5-dimethyl-2-[2-chloro-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-3-pyridylsulfonylamide,  
 (237) N-[4, 5-dimethyl-2-[2-chloro-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-3-pyridylsulfonylamide,  
 (238) 3-methyl-4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4-chloro-5-methylphenoxy]methyl]cinnamic acid,  
 (239) N-[4, 5-dimethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-2-pyridylsulfonylamide,

(240) N-[4, 5-dimethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-2-pyridylsulfonylamide,  
 (241) N-[4, 5-dimethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-3-pyridylsulfonylamide,  
 (242) 3-chloro-4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl]cinnamic acid,  
 (243) N-[4-chloro-5-methyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-2-pyridylsulfonyl-  
 5 amide,  
 (244) N-[4-chloro-5-methyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-2-pyridylsulfonyl-  
 amide,  
 (245) N-[4, 5-dimethyl-2-[2-methyl-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy] phenyl]-N-isopropyl-2-pyridyl-  
 sulfonylamide,  
 10 (246) N-[4, 5-dimethyl-2-[2-methyl-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy] phenyl]-N-isobutyl-3-pyridyl-  
 sulfonylamide,  
 (247) N-[4, 5-dimethyl-2-[2-methoxy-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-2-pyridylsulfonylamide,  
 (248) N-[4, 5-dimethyl-2-[2-methoxy-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-2-pyridylsulfonylamide,  
 (249) N-[4, 5-dimethyl-2-[2-methoxy-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy] phenyl]-N-isobutyl-2-pyridyl-  
 15 sulfonylamide, and  
 (250) N-[4, 5-dimethyl-2-[2-methoxy-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy] phenyl]-N-isopropyl-2-pyri-  
 dylsulfonylamide.

**[0026]** In the compound of formula (IA) — (IK), most preferable EP<sub>1</sub> antagonists are following compounds.

- 1) 6-[(2S, 3S)-3-(4-chloro-2-methylphenylsulfonylaminomethyl)-bicyclo[2.2.2] octan-2-yl]-5Z-hexenoic acid (the compound A),
- 2) 4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl]benzoic acid (the compound B),
- 25 3) 4-[2-[N-isobutyl-2-furanylsulfonylamino]-5-trifluoromethylphenoxy]methyl] cinnamic acid (the compound C),
- 4) 4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]benzoic acid (the compound D),
- 5) 3-methyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]benzoic acid (the compound E),
- 30 6) 4-[6-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl] cinnamic acid (the compound F),
- 7) 3-methyl-4-[6-[N-isobutyl-N-(4-methyl-2-thiaolylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid (the compound G),
- 8) 4-[4, 5-dimethyl-2-[N-(5-methyl-2-furylsulfonyl)-N-propylamino] phenoxy]methyl]benzoic acid (the compound H),
- 9) 4-[5-trifluoromethyl-2-[N-(5-methyl-2-furylcarbonyl)-N-isopropylamino] phenoxy]methyl]cinnamic acid (the compound J) and
- 35 10) 4-[6-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl] benzoic acid (the compound K).

**[0027]** The compound A was described in the specification of EP 878465 as Example 2c.

**[0028]** The compound C was described in the specification of WO 98/27053 as Example 18(9).

40 **[0029]** The compounds B, D, E, F, G, H, J and K are contained in the compound of formula (IK). These compounds were also contained in the compound of formula (IB), but they were not specifically described in the specification of WO 98/27053.

**[0030]** Although the chemical structures of all compounds were different each other, these compounds had this activity in common, and so, it became clear that an antagonism for EP<sub>1</sub> receptor lead to the treatment and/or prevention of depression.

45 **[0031]** It have been known that EP<sub>1</sub> antagonist could be used as an analgesic, an antipyretic, a therapeutic agent of frequent urination, and an anticancer agent by antagonizing EP<sub>1</sub>, however it have not been known that EP<sub>1</sub> antagonists have an antidepressive activity, and it was firstly demonstrated by this invention.

50 **[0032]** The depression in this invention is contained depression and a depressed state, for example, endogenous depression, reactive depression, weatherability depression, and neurological depressed state, the depressed state of brain organic mental disorder.

[Process for the preparation of the present invention]

55 **[0033]** The compound of formula (IA), (IB), (IC), (ID), (IE), (IF), (IG), (IH) and (IJ) may be prepared by each method described in the specification of W098/27053, EP878465, W092/19617, W096/06822, W097/00863, W099/47497, W000/20371, W02001/19814 and W02001/19819.

**[0034]** The compound of formula (IK) may be prepared by a method described in the specification of W098/27053,

or by a following method. A detailed process for the preparation is described hereinafter.

[0035] In the scheme, R is C1-4 alkyl, Tf is trifluoromethanesulfonyl, the other symbols are as hereinbefore defined.

R: C1-4 alkyl,

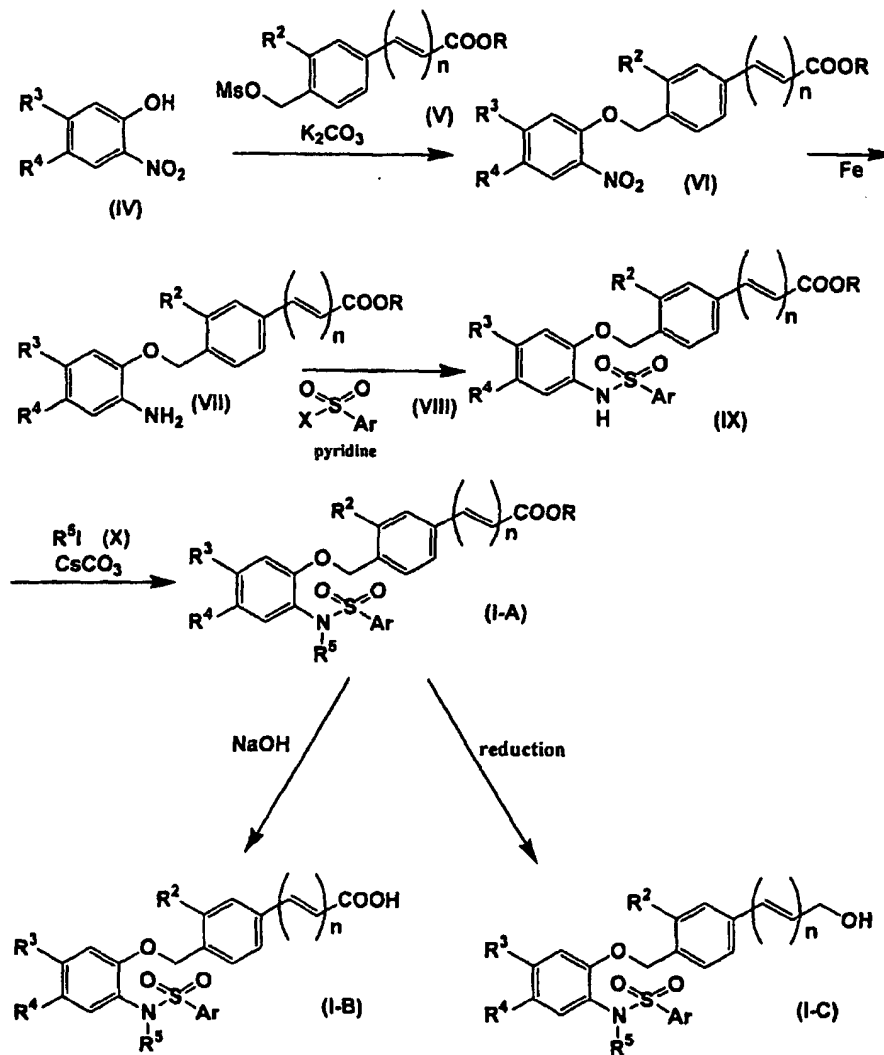
Ms: mesyl,

Tf<sub>2</sub>O: trifluoromethanesulfonic acid anhydrous,

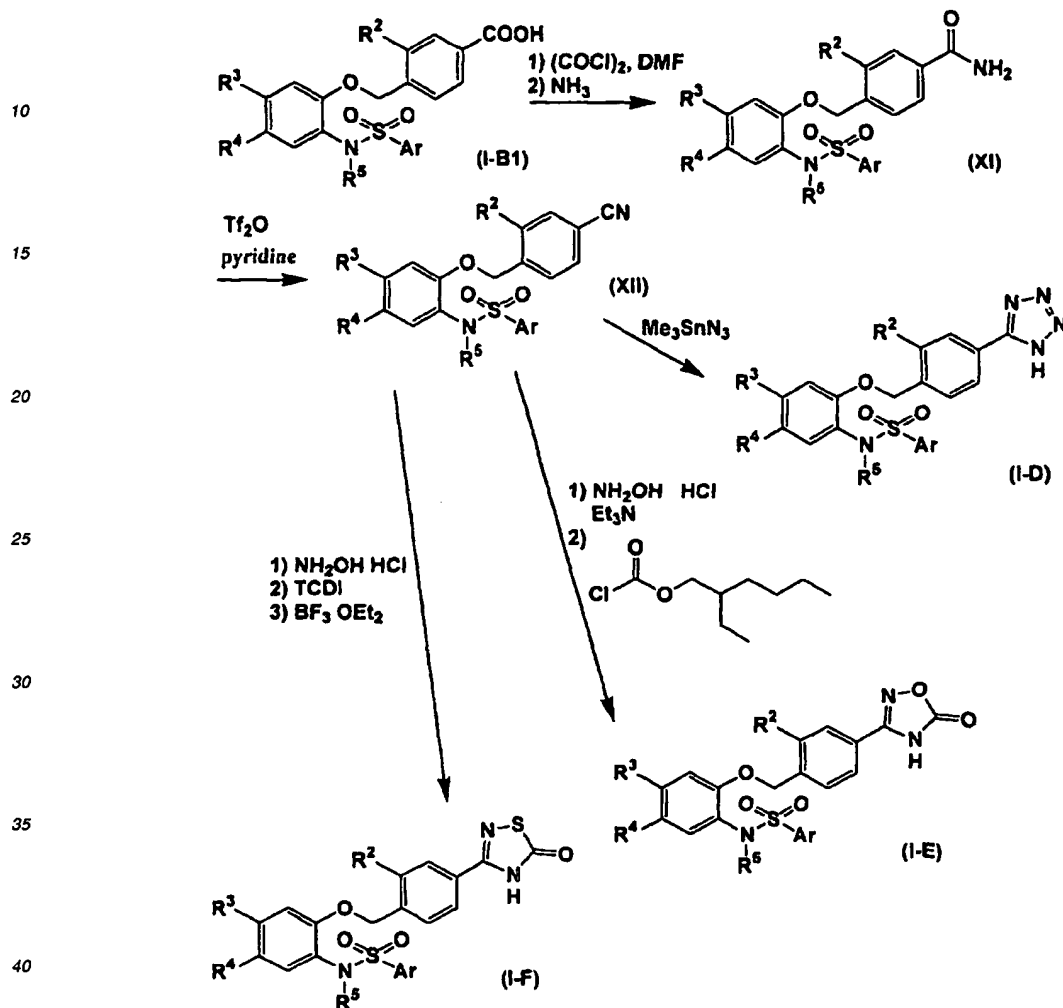
Et: ethyl,

TCDI: 1,1'-thiocarbonyldiimidazole.

Scheme (A)



Scheme (B)



[0036] Concretely, the compound B, the compound D, the compound E, the compound F, the compound G, the compound H, the compound J and the compound K were prepared by a method described in following Example. The compound B Example 2(2), the compound D : Example 2(6), the compound E : Example 2, the compound F : Example 2(32), the compound G : Example 2(74), the compound H : Example 5(30), the compound J : Example 7, the compound K : Example 2(71).

[Pharmacological Activities]

[0037] It was confirmed by the following experiments that the compounds of formula of (IA) - (IK) could be useful for the treatment of depression. The following paper can be referred to about a tail-suspension test and its testing system in mice.

1) Psychopharmacology (1985) 85: 367-370

2) Prog. Neuro-Psychopharmacol. & Biol. Psychiat. 1987 Vol. 11, 659-671

## (1) Tail-suspension test in mice

**[0038]** The test compound (10 mg/kg animal body weight) was administered orally to male ddy mice weighing around 30 g 1 hour before the beginning of measurement. The mice were suspended by their tail on the hook of Tail Suspension TEST System (Neuroscience, Inc., Model NS-TST01-SS2) using adhesive tape. The subsequent immobility time for 10 minutes was measured. If the mice have none of administration, they get about 300 seconds as an immobility time in this experiment. Generally, the medicine having an anti-depressive action shortens this immobility time.

**[0039]** The result was as follows. In addition, in any case, ten animals were used for each group.

Table 1

Compounds	Immobility time (sec.)	Inhibition (%)
Vehicle	290±33	0.0
Compound A	202±20	30±7*
Compound B	194±23	35±8**
Compound C	212±20	23±7*
Compound D	217±24	27±8*
Compound E	185±36	38±12*
Compound F	160±26	47±9**
Compound G	206±35	31±12*

(\*:  $p < 0.05$ , \*\*:  $p < 0.01$ , \*\*\*:  $p < 0.001$  vs. vehicle / Student's t test)

## (Discussion)

**[0040]** Immobility time in compounds A, B, C, D, E, F and G were shortened as compared with that in the vehicle treated group, and each rate of inhibition was statistically significant. Although the chemical structures of these compounds were different structure each other, all of them had EP<sub>1</sub> receptor antagonistic activity, and shortened the immobility state induced by tail-suspension, and these results clearly indicate that compounds having EP<sub>1</sub> antagonistic activity have an action increasing mobility, namely an anti-depressive action.

## (2) Forced swim test in rats

**[0041]** The seven-week old male SD (IGS) rat freely fed was solely put into the forced swimming equipment (the cylinder (Neuroscience, Inc.) of diameter of inner 19 cm, and height 40 cm, depth-sounding 17 cm, water temperature of 23±1 °C) manufactured with the transparent acrylics board, and let it swim for 15 minutes. The rat was immediately dried after the end of trial and was returned to the home cage. At the same time of the next day the rats were exposed to the same conditions, and behavior of rats were observed for 5 minutes. In this time, the behavior of rat is distinguished by immobile state, struggling, submerging and swimming. The immobility time, period that rats were floating on the water by taking their head outside of the water without stroking by both legs, were measured. In addition, the water in equipment was exchanged for every trial. Moreover, one trial was conducted for each animal.

**[0042]** The test compound was administered orally by 5 mL/kg dosage immediately after the end of the examination on the 1st, and 1 hour before the examination on the 2nd. And, the positive control compound (desipramine; selective serotonin reuptake inhibitor) was similarly administered intraperitoneally by 2 mL/kg dosage immediately after the end of the examination on the 1st, and 1 hour before the examination on the 2nd.

**[0043]** The result was as follows. In addition, in any case, twelve animals were used for each group.

Table 2

Compounds	Compounds	Immobility time (sec.)	Inhibition (%)
Vehicle		236±14	0±6
Desipramine		112±15	53±6***
Compound B		163±21	31±9***
Compound G		193±13	18±5*
Compound H		156±21	35±9**

Table 2 (continued)

Compounds	Compounds	Immobility time (sec.)	Inhibition (%)
Compound J		194±16	20±7*
Compound K		172±17	29±7**

(\*: p&lt;0.05, \*\*: p&lt;0.01, \*\*\*: p&lt;0.001 vs. vehicle / Student's t test)

## (Discussion)

[0044] Immobility time in compounds B, G, H, J and K group were shortened as compared with that in the vehicle treated group, and each rate of inhibition was statistically significant. Although the chemical structures of these compounds were different structure each other, all of them had EP<sub>1</sub> receptor antagonistic activity, and so, it became clear that these compounds shortened the immobility state induced by forced swim by antagonizing to EP<sub>1</sub> receptor, and showed the action to increase the mobility, namely an anti-depressive action.

## [Toxicity]

[0045] The toxicity of the compounds of the present invention is very low and therefore, it is confirmed that these compounds are safe for use as medicine. For example, LD<sub>50</sub> values of the compound A and B of the present invention by oral administration to mouse are 2000 mg/kg and over.

## Industrial Applicability

## [Application for Pharmaceuticals]

[0046] The compounds of the formula (IA) — (IK) or a non-toxic salt thereof have EP<sub>1</sub> receptor antagonistic activity, therefor, they are useful as antidepressant.

[0047] For the purpose described above, the compounds of formula (IA) — (IK) of the present invention or a non-toxic salt thereof may be normally administered systemically or topically, usually by oral or parenteral administration.

[0048] The compound of formula (IA) — (IK) or a non-toxic salt thereof may be administered in combination with other medicaments for the purpose of

- 1) complement and/or enhancement of preventing and/or treating effect,
- 2) improvement of dynamics and absorption of the compound, and lowering of dose, and/or
- 3) alleviation of side effect of the compound.

[0049] The compound of formula (IA) — (IK) may be administered in combination with other medicaments as a composition in one drug product comprising these components, or may be administered separately. When they are administered independently, they may be administered simultaneously or with time lag. Administering with time lag includes the method of administering the compound of formula (IA) — (IK) before other medicaments and vice versa, and they may be administered in the same route or not.

[0050] The above combination takes effects on whichever disease treating and/or preventing effect of the compound of formula (IA) — (IK) is complemented and/or enhanced.

[0051] As other medicaments to complement and/or to enhance the preventing and/or treating effect of an EP<sub>1</sub> antagonist of formula (IA) — (IK) for depression, for example, antianxiety agent such as series of benzodiazepine, thienodiazepine or non-benzodiazepine; antidepressant such as monoamine releasing agent, monoamine oxidase inhibitor, monoamine reuptake inhibitor (e.g. SNRI (Serotonin-Noradrenaline Reuptake Inhibitor), SSRI (Selective Serotonin Reuptake Inhibitor)), dopamine (D<sub>2</sub>) antagonist, CRF antagonist,  $\beta_3$  agonist, neurotensin antagonist, NK<sub>1</sub> antagonist, tricyclic antidepressant, tetracyclic antidepressant; anticholinergic agent, affinity polyacryl resin, obstipant, mucosal paralyzant, bulk cathartic, saline purgative, fibrillose preparation, drug for controlling intestinal function, automatic nervous regulator, calcium antagonist, phosphodiesterase inhibitor, serotonin antagonist (e.g. 5-HT<sub>3</sub> antagonist, 5-HT<sub>4</sub> antagonist), serotonin agonist (e.g. 5-HT<sub>4</sub> agonist, 5-HT<sub>1A</sub> agonist), gastrointestinal regulator (e.g. CCK-A antagonist,  $\beta_3$  agonist, neurotensin antagonist, opioid agonist, NK<sub>1</sub> antagonist, NK<sub>2</sub> antagonist, 5-HT<sub>1A</sub> agonist, muscarine agonist, 5-lipoxygenase inhibitor, CRF antagonist) are given.

[0052] As antianxiety agent, for example, alprazolam, oxazepam, oxazolam, tandospirone citrate, clobazepam, clonazepam, clorazepate dipotassium, chlordiazepoxide, diazepam, tofisopam, prazepam, fludiazepam, flutazolam, flutoprazepam, bromazepam, mexazolam, medazepam, ethyl loflazepate, lorazepam are given.

**[0053]** As antidepressant, for example, dosulepin hydrochloride, ethyl loflazepate, progabide, etizolam, setipiline maleate, minaprine dihydrochloride, amoxapine, lofepramine hydrochloride, maprotiline hydrochloride, mianserin hydrochloride, G-34586, MD-690276, FCE-20124, modafinil, RV-12309, S-1574, bupropion, venlafaxine hydrochloride, tandospirone citrate, paroxetine hydrochloride, trazodone hydrochloride, risperidone, milnacipran hydrochloride, citalopram hydrobromide, fluvoxamine maleate, mirtazapine, topiramate, nefazodone hydrochloride, moclobemide, sertraline hydrochloride, OR-611, lamotrigine, olanzapine, pramipexole hydrochloride, fluoxetine hydrochloride, LU-26-054, tomoxetine hydrochloride, BMV-13805-1, duloxetine hydrochloride, MD-370503, BIMT-17, CP-93393, L-759274, LAX-101c are given.

**[0054]** As SSRI (Selective Serotonin Reuptake Inhibitor), for example, minaprine dihydrochloride, sibutramine hydrochloride, tramadol hydrochloride, venlafaxine hydrochloride, WY-45030, paroxetine hydrochloride, milnacipran hydrochloride, citalopram hydrobromide, fluvoxamine maleate, nefazodone hydrochloride, sertraline hydrochloride, fluoxetine hydrochloride, LU-26-054, duloxetine hydrochloride are given.

**[0055]** As dopamine antagonist, for example, amoxapine, etizolam, spiperone, sulpiride, timiperone, domperidone, nemonapride, haloperidol, fluphenazine, prochlorperazine, propericiazine, bromperidol, risperidone, clebopride malate, itopride hydrochloride, sultopride hydrochloride, tiapride hydrochloride, mosapramine hydrochloride, oxypertine, zotepine, pimozide, mazindol, indeloxazine hydrochloride, dosulepine hydrochloride, mazaticol hydrochloride are given.

**[0056]** As CRF antagonist, for example, DPC-368, NBI-34041, NBI-37582 are given.

**[0057]** As  $\beta_3$  agonist, for example, SR-58611A, AJ-9677, KUL-7211, SB-418790, GW-427353, N-5984 are given.

**[0058]** As NK<sub>1</sub> antagonist, for example, ezlopitant, MK-869, CP-122721, DNK-333, L-758298, NKP-608, SR-140333, TAK-637, CS-003 are given.

**[0059]** As NK<sub>2</sub> antagonist, for example, saredutant, nepadutant, DNK-333, CS-003 are given.

**[0060]** As tricyclic antidepressant, for example, amoxapine, setipiline maleate, trimipramine maleate, amitriptyline hydrochloride, imipramine hydrochloride, clomipramine hydrochloride, desipramine hydrochloride, dosulepine hydrochloride, nortriptyline hydrochloride, mianserin hydrochloride, lofepramine hydrochloride are given.

**[0061]** As tetracyclic antidepressant, for example, mianserin hydrochloride, setipiline maleate, maprotiline hydrochloride are given.

**[0062]** As anticholinergic agent, for example, aniracetam, etomidoline, tofisopam, dimetotiazine mesylate, scopolamine butylbromide, oxapium iodide, diphenylpiperidinomethylidioxolane iodide, tiemonium iodide, scopolia extract, trospium chloride, oxyphenyclimine hydrochloride, cyclopentolate hydrochloride, dicycloverine hydrochloride, trihexyphenidyl hydrochloride, pirenzepine hydrochloride, piroheptine hydrochloride, propiverine hydrochloride, mazaticol hydrochloride, metixene hydrochloride, ipratropium bromide, pipethanate ethobromide, oxitropium bromide, glycopyrronium bromide, tiqizium bromide, timepidium bromide, scopolamine butylbromide, butropium bromide, prifinium bromide, flutropium bromide, propantheline bromide, anisotropine methylbromide, methylbenactyzium bromide, mepenzolate bromide, scopolamine hydrobromide, homatropine hydrobromide, N-methylscopolamine sulfate, atropine sulfate are given.

**[0063]** As obstipant, for example, albumin tannate, bismuth subnitrate, bismuth subgallate are given.

**[0064]** As mucosal paralyzant, for example, oxethazaine, stocain, topicain are given.

**[0065]** As bulk cathartic, for example, carmellose sodium (carboxy methylcellulose sodium) is given.

**[0066]** As saline purgative, magnesium oxide, magnesium sulfate, magnesium carbonate are given.

**[0067]** As calcium antagonist, for example, verapamil, nifedipine, diltiazem, nicardipine, nilvadipine are given.

**[0068]** As phosphodiesterase inhibitor, for example, cilostazol, amrinone, anagrelide hydrochloride, enoxymon, olprinone hydrochloride, pimobendan, milrinone, doxofylline, sildenafil citrate, mopidamol, toborinone, tadalafil, vardenafil, MCI-154, cilomilast, roflumilast are given.

**[0069]** As serotonin antagonist, for example, ketanserin tartarate, mosapramine hydrochloride, zotepine, ondansetron hydrochloride, tropisetron hydrochloride, risperidone, granisetron hydrochloride, sarpogrelate hydrochloride, perospirone hydrochloride hydrate, mirtazapine, ramosetron hydrochloride, azasetron hydrochloride, nefazodone hydrochloride, olanzapine, quetiapine fumarate, ziprasidone hydrochloride hydrate, dolasetron mesylate, clozapine, alosetron hydrochloride, indisetron hydrochloride, RS-25259-197, HP-873, EGIS-3886, itasetron hydrochloride, KC-9946, F-0930-RS, blonanserin, BIMT-17 are given.

**[0070]** As serotonin agonist, for example, buspirone hydrochloride, tandospirone citrate, sumatriptan succinate, mosapride citrate, naftopidil, LAS-17177, mirtazapine, naratriptan hydrochloride, zolmitriptan, rizatriptan benzoate, eletriptan hydrobromide, LAS-31416, tegaserod maleate, VML-251, BMV 13805-1, xaliproden hydrochloride, repinotan hydrochloride are given.

**[0071]** As CCK-A antagonist, for example, loxiglumide, dexloxiglumide, lintitript, devacard, Z-203 are given.

**[0072]** As 5-lipoxygenase inhibitor, for example, oxatomide, diruton, ML-3000, darbufelone mesylate, DUP-654, LDP-977 are given.

**[0073]** Weight ratio of the compound of formula (IA) — (IK) and other medicaments is not limited.

**[0074]** A combination of any two or more of other medicaments may be administered.

**[0075]** A combination of any two or more of the compound of formula (IA) — (IK) may be administered.

**[0076]** In other medicaments to complement and/or to enhance the preventing and/or treating effect of the compound of formula (IA) — (IK), medicaments that not only exist now but also may be found in the future on the basis of above mechanisms are included.

**[0077]** For the purpose described above, the compound of formula (IA) — (IK) or a salt thereof of the present invention or a concomitant drug combined the compound of formula (IA) — (IK) with other medicaments may be normally administered systemically or topically, usually by oral or parenteral administration.

**[0078]** The doses to be administered are determined depending upon, for example, age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment, etc. In the human adult, the doses per person at a time are generally from 1 mg to 1000 mg, by oral administration, up to several times per day, and from 1 mg to 100 mg, by parenteral administration (preferably intravenous administration), up to several times per day, or continuous administration between 1 and 24 hours per day into vein.

**[0079]** As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases where-in doses lower than or greater than the ranges specified above may be used.

**[0080]** The compound of formula (IA) — (IK) or a salt thereof or concomitant drug combined the compound of formula (IA) — (IK) with other medicaments may be administered in the composition of, for example, solid compositions, liquid compositions or other compositions each for oral administration, or injections, liniments or suppositories, each for parenteral administration.

**[0081]** Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders and granules.

**[0082]** Capsules include hard capsules and soft capsules.

**[0083]** In such solid forms, one or more of the active compounds may be admixed with vehicles such as lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone or magnesium aluminometasilicate. The compositions may comprise, in accordance with the conventional process, additives other than the inert diluent, for example, lubricants such as magnesium stearate; disintegrants such as cellulose calcium glycolate; stabilizer such as lactose; and solubilizing agent such as glutamic acid or aspartic acid. Tablets or pills may be coated with a film of a gastric soluble or enteric substance such as sucrose, gelatin, hydroxypropyl cellulose or hydroxypropyl methylcellulose phthalate, or with two or more layers, if necessary. Furthermore, capsules made of a substance which can be absorbed in the body, for example, gelatin, are included.

**[0084]** Liquid forms for oral administration include pharmaceutically acceptable solutions, suspensions and emulsions, syrups and elixirs. In such forms, one or more of the active compounds may be dissolved, suspended or emulsified into diluents commonly used in the art (such as purified water, ethanol). Besides such liquid forms may also comprise some additives, such as wetting agents, suspending agents, sweetening agents, flavoring agents, aroma or preservative.

**[0085]** The other compositions for oral administration include sprays which comprise one or more active compounds and are formulated in a manner known per se in the art. The compositions may comprise, in addition to an inert diluent, a stabilizer such as sodium bisulfite and a tonicity agent such as sodium chloride, sodium citrate or citric acid. The preparation process of sprays is described in detail in, for example, U.S. Patent Nos. 2,868,691 and 3,095,355.

**[0086]** In the present invention, injections for parenteral administration include sterile aqueous and/or non-aqueous solutions, suspensions and emulsions. The aqueous solutions or suspensions include, for example, distilled water for injection and saline. The non-aqueous solutions or suspensions include propylene glycol, polyethylene glycol, vegetable oils such as olive oil, alcohol such as ethanol and Polysorbate 80 (trade mark). Furthermore, sterile aqueous and non-aqueous solutions, suspensions, and emulsions may be used in combination. Such compositions may additionally comprise adjuvants such as antiseptic, humectant, emulsifier, dispersant, stabilizer (such as lactose) and solubilizing agent (such as glutamic acid and aspartic acid). They are sterilized by filtration through a bacteria retaining filter, the addition of a fungicide, or irradiation. Also, a sterile solid composition is prepared and then, for example, a freeze-dried product may be dissolved in sterilized or sterile distilled water for injection or another sterile solvent before use.

**[0087]** The other compositions for parenteral administration include liquids for external use, ointments, endemic liniments, suppositories for intrarectal administration and pessaries for vaginal administration which comprise one or more of the active substances and may be prepared by methods known per se.

**[0088]** The compounds of the present invention may be administered in the form of, for example, solid compositions, liquid compositions or other compositions for oral administration, injections, liniments or suppositories for parenteral administration.

**[0089]** Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders and granules. Capsules include hard capsules and soft capsules.

**[0090]** In such solid forms, one or more of the active compound(s) may be admixed with vehicles (such as lactose, mannitol, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone or magne-



sium aluminometasilicate). The compositions may comprise, in accordance with the conventional process, additives other than the inert diluent, for example, lubricants such as magnesium stearate, disintegrants such as cellulose calcium glycolate, and solubilizing agent such as glutamic acid or aspartic acid. Tablets or pills may be coated with a film of a gastric soluble or enteric substance such as sucrose, gelatin, hydroxypropyl cellulose or hydroxypropyl cellulose phthalate, or with two or more layers, if necessary. Furthermore, capsules made of a substance which can be absorbed in the body, for example, gelatin, are included.

[0091] Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, syrups and elixirs. Such liquid compositions comprise one or more of the active substance(s) and an ordinarily employed inert diluent(s) (such as purified water or ethanol) dissolving the substance(s) therein. The compositions may comprise, in addition to the inert diluent, an adjuvant such as humectants or suspending agents, sweetening agents, flavoring agents, aromatic agents and antiseptics.

[0092] The other compositions for oral administration include sprays which comprise one or more active substances and are formulated in a manner known per se in the art. The compositions may comprise, in addition to an inert diluent, a stabilizer such as sodium bisulfite and a tonicity agent such as sodium chloride, sodium citrate or citric acid. The preparation process of sprays is described in detail in, for example, U.S. Patent Nos. 2,868,691 and 3,095,355.

[0093] In the present invention, injections for parenteral administration include sterile aqueous and/or non-aqueous solutions, suspensions and emulsions. The aqueous solutions or suspensions include, for example, distilled water for injection and saline. The non-aqueous solutions or suspensions include propylene glycol, polyethylene glycol, vegetable oils such as olive oil, alcohol such as ethanol and Polysorbate 80 (trade mark). Furthermore, sterile aqueous and non-aqueous solutions, suspensions, and emulsions may be used in combination. Such compositions may additionally comprise adjuvants such as antiseptic, humectant, emulsifier, dispersant, stabilizer and solubilizing agent (such as glutamic acid and aspartic acid). They are sterilized by filtration through a bacteria retaining filter, the addition of a fungicide, or irradiation. Also, a sterile solid composition is prepared and then, for example, a freeze-dried product may be dissolved in sterilized or sterile distilled water for injection or another sterile solvent before use.

[0094] The other compositions for parenteral administration include liquids for external use, ointments, endermic liniments, suppositories for intrarectal administration and pessaries for vaginal administration which comprise one or more of the active substances and may be prepared by methods known per se.

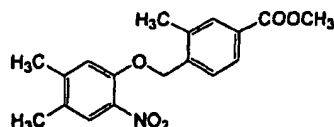
Best mode for carrying out the invention

[0095] The following Reference examples and Examples are intended to illustrate, but not to limit the present invention.

[0096] The solvents in parentheses at chromatographic separations section show the developing or eluting solvents and the ratios of the solvents used are indicated by volume. Without special explanation, NMR data was determined in  $\text{CDCl}_3$  solution. And the solvents in parentheses at NMR data section show solvents used in determination.

Reference example 1

4-(2-nitro-4,5-dimethylphenoxy)methyl-3-methylbenzoic acid methyl ester



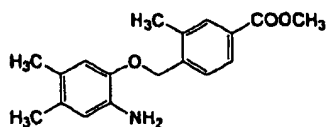
[0098] Under atmosphere of argon, a mixture of 2-nitro-4,5-dimethylphenol (4 g), DMF (100 ml), potassium carbonate (6.6 g) and 4-mesyloxymethyl-3-methylbenzoic acid methyl ester (6.8 g) were stirred for 15 minutes at 60 °C. After the termination of reaction, the mixture was cooled and poured into iced water. The mixture was extracted with ethyl acetate - hexane. The organic layer was washed, dried, concentrated under reduced pressure to give the title compound (7.22 g) having the following physical data.

TLC: Rf 0.24 (n-hexane: ethyl acetate =4:1).

## Reference example 2

4-(2-amino-4,5-dimethylphenoxy)methyl-3-methylbenzoic acid methyl ester

[0099]



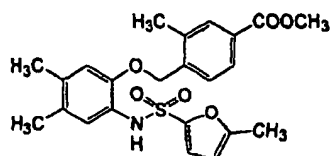
[0100] A mixture of 4-(2-nitro-4,5-dimethylphenoxy)methyl-3-methylbenzoic acid methyl ester prepared in reference example 1 (7.21 g), acetic acid (88 ml) and water (8.8 ml) was stirred at 50 °C. To the reaction solution, iron powder (6.11 g) was gradually added, and the mixture was stirred for 1 hour at 50 °C. After cooling, the mixture was filtered and the filtrate was concentrated and azeotroped with toluene. To the residue, ethyl acetate water (100 ml - 100 ml) was added and the mixture was filtrated over Celite (registered trademark). The organic layer was washed, dried, concentrated under reduced pressure to give the title compound (4.66 g) having the following physical data.

TLC : Rf 0.51 (n-hexane : ethyl acetate = 2 : 1).

## Reference example 3

3-methyl-4-[2-[N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy)methyl]benzoic acid methyl ester

[0101]



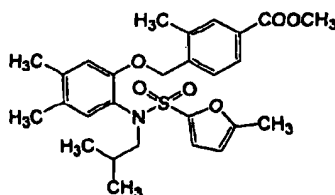
[0102] A solution of 4-(2-amino-4,5-dimethylphenoxy)methyl-3-methylbenzoic acid methyl ester prepared in reference example 2 (632 mg) in pyridine (4 ml) was cooled to 0°C, then 5-methylfuran-2-sulfonyl chloride (490 mg) was added dropwise thereto. After the solution was stirred for 1 hour at room temperature, the reaction mixture was diluted by ethyl acetate, and poured into water. The organic layer was washed, dried, concentrated under reduced pressure. The residue was washed by mixed solvent of diisopropylether and hexane to give the title compound (875 mg) having the following physical data.

TLC : Rf 0.42 (n-hexane : ethyl acetate = 2 : 1).

## Example 1

3-methyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy)methyl]benzoic acid methyl ester

[0103]



**[0104]** To a solution of 3-methyl-4-[2-[N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]benzoic acid methyl ester prepared in reference example 3 (870 mg) in N,N-dimethylacetamide (2 ml), cesium carbonate (1.37 g) and isobutyl iodide (0.36 ml) were added and the mixture was stirred for 1 hour at 100 °C. The reaction mixture was allowed to cool and poured into ethyl acetate - water (40 ml - 40 ml). The organic layer was washed, dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (toluene - ethyl acetate) to give the title compound (855 mg) having the following physical data.

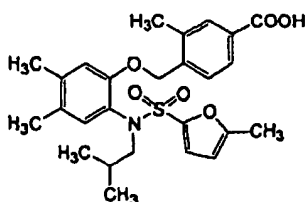
TLC: Rf 0.51 (n-hexane: ethyl acetate = 2 : 1);

NMR :  $\delta$  7.87 (d, J = 8.4 Hz, 1H), 7.86 (s, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.04 (s, 1H), 6.70 (m, 2H), 5.93 (m, 1H), 4.91 (brs, 2H), 3.92 (s, 3H), 3.48 (m, 2H), 2.34 (s, 3H), 2.23 (s, 3H), 2.18 (s, 3H), 2.09 (s, 3H), 0.90 (brs, 6H).

#### Example 2

3-methyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]benzoic acid

**[0105]**



**[0106]** To a solution of 3-methyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]benzoic acid methyl ester prepared in example 1 (850 mg) in dioxane (10 ml), 2N aqueous sodium hydroxide (2.5 ml) and methanol (4 ml) were added, and the mixture was stirred for 30 hours at room temperature. To the mixture, 2N hydrochloric acid was added, then ethyl acetate — water (30 ml - 15 ml) was also added. The organic layer was washed, dried and concentrated under reduced pressure. The residue was dissolved in hot ethanol (40 ml) and added by hot water (40 ml), then allowed to cool. Precipitation was filtrated, and dried to give the title compound (755 mg) having the following physical data.

TLC : Rf 0.78 (chloroform : methanol: water = 8 : 2 : 0.2);

NMR :  $\delta$  7.94 (d, J = 7.8 Hz, 1H), 7.93 (s, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.04 (s, 1H), 6.74-6.70 (m, 2H), 5.94 (dd, J = 3.3, 0.9 Hz, 1H), 4.94 (br, 2H), 3.48 (d, J = 6.6 Hz, 2H), 2.37 (s, 3H), 2.24 (s, 3H), 2.19 (s, 3H), 2.11 (s, 3H), 1.68 (sep, J = 6.6 Hz, 1H), 0.91 (d, J = 6.6 Hz, 6H).

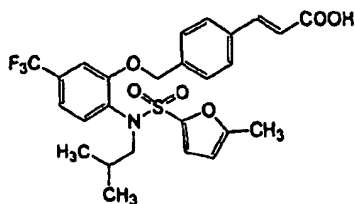
Example 2(1) ~ Example 2(124)

**[0107]** By the same procedures as described in reference example 1 → reference example 2 → reference example 3 → example 1 → example 2 using corresponding compounds, the title compounds having the following physical data were obtained.

## Example 2(1)

4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl cinnamic acid

[0108]



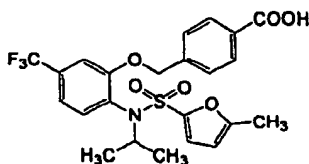
TLC: Rf 0.51 (n-hexane: ethyl acetate: acetic acid = 1:1: 0.02);

NMR:  $\delta$  7.80 (d, J = 16.2 Hz, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.45 - 7.36 (m, 3H), 7.26 (dd, J = 8.2, 1.8 Hz, 1H), 7.18 (d, J = 1.8 Hz, 1H), 7.00 - 5.00 (br, 1H), 6.75 (d, J = 3.4 Hz, 1H), 6.49 (d, J = 16.2 Hz, 1H), 5.98 (dq, J = 3.4, 0.8 Hz, 1H), 5.05 (brs, 2H), 3.51 (d, J = 7.4 Hz, 2H), 2.16 (s, 3H), 1.75 - 1.50 (m, 1H), 0.88 (d, J = 6.8 Hz, 6H).

## Example 2(2)

4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl benzoic acid

[0109]



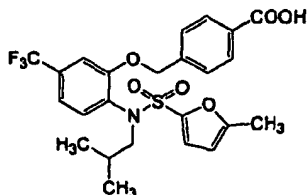
TLC: Rf 0.44 (chloroform: methanol = 9: 1);

NMR:  $\delta$  8.16 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.21-7.26 (m, 3H), 6.84 (d, J = 3.2 Hz, 1H), 6.05 (m, 1H), 5.21 (m, 2H), 4.49 (m, 1H), 2.33 (s, 3H), 1.10 (d, J = 6.6 Hz, 6H).

## Example 2(3)

4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl benzoic acid

[0110]



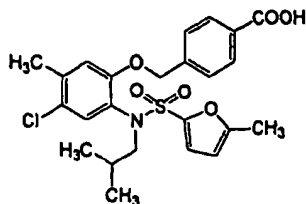
TLC: Rf 0.46 (chloroform: methanol = 9: 1);

NMR:  $\delta$  8.15 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 8.6 Hz, 2H), 7.41 (m, 1H), 7.29 (m, 1H), 7.18 (m, 1H), 6.76 (d, J = 3.4 Hz, 1H), 5.98 (m, 1H), 5.10 (s, 2H), 3.51 (d, J = 6.2 Hz, 2H), 2.16 (s, 3H), 1.64 (m, 1H), 0.90 (d, J = 6.8 Hz, 6H).

Example 2(4)

4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4-chloro-5-methylphenoxy]methyl] benzoic acid

[0111]



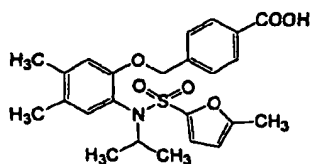
TLC : Rf 0.30 (chloroform : methanol = 9:1);

NMR :  $\delta$  8.12 and 7.46 (each d, J = 8.1 Hz, each 2H), 7.20 (s, 1H), 6.81-6.75 (m, 2H), 6.01-5.98 (m, 1H), 5.12-4.98 (m, 2H), 3.45 (d, J = 7.5 Hz, 2H), 2.34 and 2.19 (each s, each 3H), 1.75-1.59 (m, 1H), 0.91 (d, J = 6.9 Hz, 6H).

Example 2(5)

4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]benzoic acid

[0112]



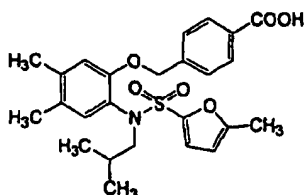
TLC: Rf 0.38 (chloroform: methanol = 10 : 1);

NMR :  $\delta$  8.12-8.09 (m, 2H), 7.56 (d, J = 8.4 Hz, 2H), 6.81 (s, 1H), 6.79 (d, J = 3.3 Hz, 1H), 6.75 (s, 1H), 6.02 (dd, J = 3.3, 1.2 Hz, 1H), 5.10 (s, 2H), 4.48 (m, 1H), 2.30 (s, 3H), 2.23 (s, 3H), 2.17 (s, 3H), 1.11 (d, J = 6.6 Hz, 6H).

Example 2(6)

4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]benzoic acid

[0113]



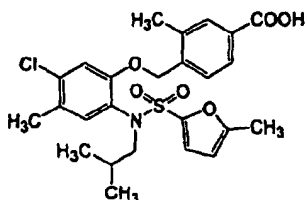
TLC : Rf 0.38 (chloroform : methanol = 10 : 1);

NMR :  $\delta$  8.12-8.08 (m, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.03 (s, 1H), 6.71 (d, J = 3.3 Hz, 1H), 6.68 (s, 1H), 5.92 (dd, J = 3.3, 0.9 Hz, 1H), 5.00 (brs, 2H), 3.52-3.46 (m, 2H), 2.22 (s, 3H), 2.18 (s, 3H), 2.13 (s, 3H), 1.68 (m, 1H), 0.91 (d, J = 6.6 Hz, 6H).

Example 2(7)

3-methyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4-methyl-5-chlorophenoxymethyl]benzoic acid

[0114]

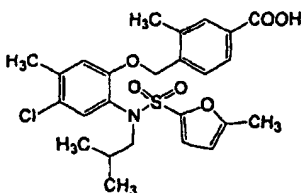


TLC : Rf 0.42 (chloroform : methanol = 9 : 1);  
NMR :  $\delta$  8.00-7.89 (m, 2H), 7.41 (d, J = 8.4 Hz, 1H), 7.16 (s, 1H), 6.95 (s, 1H), 6.74 (d, J = 3.3 Hz, 1H), 5.96 (m, 1H), 4.94 (s, 2H), 3.47 (d, J = 6.3 Hz, 2H), 2.37 (s, 3H), 2.30 (s, 3H), 2.11 (s, 3H), 1.64 (m, 1H), 0.90 (d, J = 6.6 Hz, 6H).

Example 2(8)

3-methyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4-chloro-5-methylphenoxymethyl]benzoic acid

[0115]

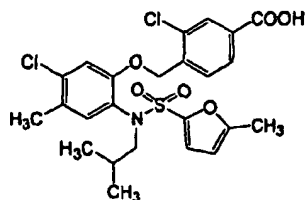


TLC : Rf 0.58 (chloroform : methanol = 9 : 1);  
NMR :  $\delta$  7.96 (d, J = 7.5 Hz, 1H), 7.94 (s, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.20 (s, 1H), 6.81 (s, 1H), 6.77 (d, J = 3.3 Hz, 1H), 6.03-5.97 (m, 1H), 4.99 (brs, 2H), 3.44 (d, J = 7.5 Hz, 2H), 2.39 (s, 3H), 2.36 (s, 3H), 2.17 (s, 3H), 1.75-1.60 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H).

Example 2(9)

3-chloro-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4-methyl-5-chlorophenoxymethyl]benzoic acid

[0116]



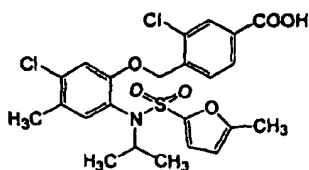
TLC: Rf 0.38 (chloroform: methanol = 9 : 1);  
NMR :  $\delta$  8.13 (d, J = 1.5 Hz, 1H), 8.02 (dd, J = 8.4, 1.5 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.15 (s, 1H), 6.94 (s, 1H), 6.76 (d, J = 3.3 Hz, 1H), 5.98 (m, 1H), 5.25-4.90 (br, 2H), 3.48 (d, J = 6.6 Hz, 2H), 2.31 (s, 3H), 2.16 (s, 3H), 1.64 (m, 1H), 0.92 (d, J = 6.6 Hz, 6H).

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## Example 2(10)

3-chloro-4-[2-[N-isopropyl-N-(5-methyl-2-furysulfonyl)amino]-4-methyl-5-chlorophenoxymethyl]benzoic acid

[0117]



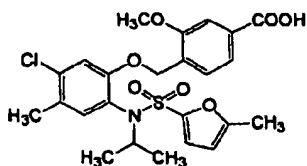
TLC : Rf 0.38 (chloroform : methanol = 9:1);

NMR :  $\delta$  8.12 (d, J = 1.5 Hz, 1H), 8.07 (dd, J = 8.4, 1.5 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 6.99 (s, 1H), 6.95 (s, 1H), 6.85 (d, J = 3.3 Hz, 1H), 6.06 (m, 1H), 5.20 (d, J = 14.4 Hz, 1H), 5.15 (d, J = 14.4 Hz, 1H), 4.48 (m, 1H), 2.33 (s, 3H), 2.30 (s, 3H), 1.11 (d, J = 6.3 Hz, 3H), 1.09 (d, J = 6.3 Hz, 3H).

## Example 2(11)

3-methoxy-4-[2-[N-isopropyl-N-(5-methyl-2-furysulfonyl)amino]-4-methyl-5-chlorophenoxymethyl]benzoic acid

[0118]



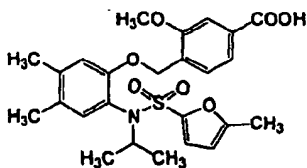
TLC: Rf 0.49 (chloroform: methanol = 9 : 1);

NMR :  $\delta$  7.78 (dd, J = 8.1, 1.5 Hz, 1H), 7.76 (d, J = 1.5 Hz, 1H), 7.59 (d, J = 1.5 Hz, 1H), 7.01 (s, 1H), 6.96 (s, 1H), 6.83 (d, J = 3.3 Hz, 1H), 6.05- 6.00 (m, 1H), 5.11 (d, J = 14.1 Hz, 1H), 5.07 (d, J = 14.1 Hz, 1H), 4.55-4.40(m, 1H), 3.94 (s, 3H), 2.30 (s, 3H), 2.29 (s, 3H), 1.12 (d, J = 6.9 Hz, 6H).

## Example 2(12)

3-methoxy-4-[2-[N-isopropyl-N-(5-methyl-2-furysulfonyl)amino]-4,5-dimethylphenoxymethyl]benzoic acid

[0119]



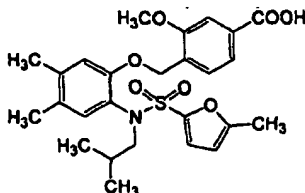
TLC : Rf 0.44 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.77 (dd, J = 8.1, 1.2 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.58 (d, J = 1.2 Hz, 1H), 6.84 (s, 1H), 6.81 (d, J = 3.3 Hz, 1H), 6.78 (s, 1H), 6.05-6.00 (m, 1H), 5.09 (s, 2H), 4.60-4.40 (m, 1H), 3.94 (s, 3H), 2.29 (s, 3H), 2.24 (s, 3H), 2.17 (s, 3H), 1.12 (d, J = 6.9 Hz, 6H).

## Example 2(13)

3-methoxy-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]benzoic acid

[0120]



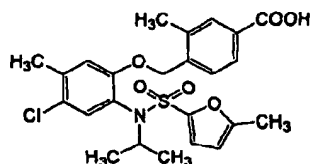
TLC : Rf 0.45 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.73 (dd, J = 8.1, 1.2 Hz, 1H), 7.58 (d, J = 1.2 Hz, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.07 (s, 1H), 6.75-6.70 (m, 2H), 5.95-5.90 (m, 1H), 5.15-4.85 (m, 2H), 3.94 (s, 3H), 3.51 (br, 2H), 2.23 (s, 3H), 2.19 (s, 3H), 2.11 (s, 3H), 1.80-1.60 (m, 1H), 0.94 (br, 6H).

## Example 2(14)

3-methoxy-4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-4-chloro-5-methylphenoxy]methyl]benzoic acid

[0121]



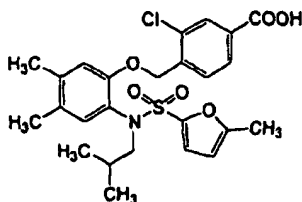
TLC : Rf 0.46 (chloroform: methanol =9:1);

NMR(DMSO- $d_6$ ) :  $\delta$  13.02 (s, 1H), 7.58-7.50 (m, 3H), 7.24 (s, 1H), 6.98 (s, 1H), 6.94 (d, J = 3.3 Hz, 1H), 6.25 (m, 1H), 5.10 (d, J = 13.5 Hz, 1H), 5.04 (d, J = 13.5 Hz, 1H), 4.24 (m, 1H), 3.87 (s, 3H), 2.34 (s, 3H), 2.27 (s, 3H), 0.99 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H).

## Example 2(15)

3-chloro-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]benzoic acid

[0122]



TLC : Rf 0.40 (chloroform : methanol = 9:1);

NMR :  $\delta$  8.12 (d, J = 1.8 Hz, 1H), 8.02 (dd, J = 8.1, 1.8 Hz, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.03 (s, 1H), 6.75 (d, J = 3.3 Hz, 1H), 6.70 (s, 1H), 5.96 (m, 1H), 5.25-4.85 (br, 2H), 3.50 (d, J = 6.6 Hz, 2H), 2.24 (s, 3H), 2.19 (s, 3H), 2.16 (s, 3H),



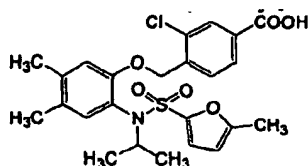
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1.79 (m, 1H), 0.93 (d, J = 6.6 Hz, 6H).

Example 2(16)

3-chloro-4-[2-[N-isopropyl-N-(5-methyl-2-furysulfonyl)amino]-4,5-dimethylphenoxy]benzoic acid

[0123]



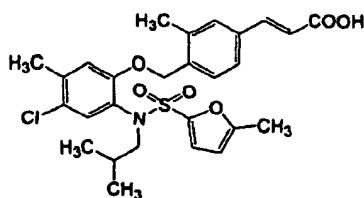
TLC : Rf 0.39 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  8.11 (d, J = 1.8 Hz, 1H), 8.06 (dd, J = 8.1, 1.8 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 6.86-6.80 (m, 2H), 6.75 (s, 1H), 6.05 (m, 1H), 5.17 (s, 2H), 4.51 (m, 1H), 2.32 (s, 3H), 2.25 (s, 3H), 2.18 (s, 3H), 1.12 (d, J = 6.6 Hz, 3H), 1.11 (d, J = 6.6 Hz, 3H).

Example 2(17)

3-methyl-4-[2-[N-isobutyl-N-(5-methyl-2-furysulfonyl)amino]-4-chloro-5-methylphenoxy]cinnamic acid

[0124]



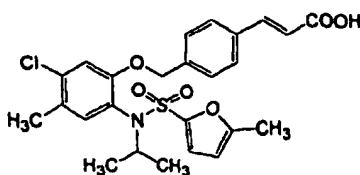
TLC : Rf 0.37 (chloroform : methanol = 9 : 1);

NMR(CD<sub>3</sub>OD) :  $\delta$  7.63 (d, J = 16.2 Hz, 1H), 7.45 (s) and 7.44 (d, J = 8.1 Hz) total 2H, 7.34 (d, J = 8.1 Hz, 1H), 7.17 (s, 1H), 7.10 (s, 1H), 6.72 (d, J = 3.3 Hz, 1H), 6.50 (d, J = 16.2 Hz, 1H), 6.08 (dd, J = 3.3, 1.2 Hz, 1H), 4.98 (brs, 2H), 3.44 (d, J = 6.9 Hz, 2H), 2.37 (s, 3H), 2.35 (s, 3H), 2.10 (s, 3H), 1.60 (m, 1H), 0.87 (d, J = 6.6 Hz, 6H).

Example 2(18)

4-[2-[N-isopropyl-N-(5-methyl-2-furysulfonyl)amino]-4-methyl-5-chlorophenoxy]cinnamic acid

[0125]



TLC: Rf 0.31 (chloroform : methanol = 9 : 1);

NMR:  $\delta$  7.73 (d, J = 15.9 Hz, 1H), 7.57 and 7.49 (each d, J = 8.1 Hz, each 2H), 6.98 and 6.92 (each s, each 1H), 6.81 (d, J = 3.3 Hz, 1H), 6.46 (d, J = 15.9 Hz, 1H), 6.03 (d, J = 3.3 Hz, 1H), 5.05 (s, 2H), 4.50-4.38 (m, 1H), 2.30 and 2.28

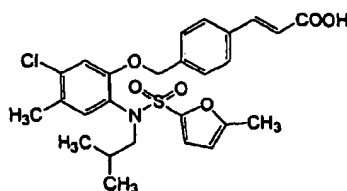
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(each s, each 3H), 1.10 and 1.09 (each d, J = 6.6 Hz, each 3H).

## Example 2(19)

4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4-methyl-5-chlorophenoxymethyl] cinnamic acid

[0126]



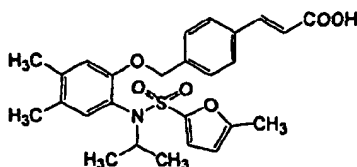
TLC: Rf 0.31 (chloroform: methanol = 9 : 1);

NMR :  $\delta$  7.77 (d, J = 15.9 Hz, 1H), 7.56 and 7.35 (each d, J = 7.8 Hz, each 2H), 7.14 and 6.92 (each s, each 1H), 6.72 (d, J = 3.6 Hz, 1H), 6.47 (d, J = 15.9 Hz, 1H), 5.95 (d, J = 3.6 Hz, 1H), 5.00-4.88 (m, 2H), 3.52-3.42 (m, 2H), 2.29 and 2.13 (each s, each 3H), 1.72-1.60 (m, 1H), 0.90 (d, J = 6.3 Hz, 6H).

## Example 2(20)

4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxymethyl] cinnamic acid

[0127]



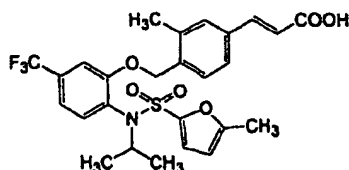
TLC : Rf 0.39 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.78 (d, J = 15.9 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 6.80 (s, 1H), 6.79 (d, J = 3.3 Hz, 1H), 6.76 (s, 1H), 6.46 (d, J = 15.9 Hz, 1H), 6.01 (m, 1H), 5.06 (s, 2H), 4.47 (sept, J = 6.6 Hz, 1H), 2.30 (s, 3H), 2.23 (s, 3H), 2.16 (s, 3H), 1.11 and 1.10 (each d, J = 6.6 Hz, each 3H).

## Example 2(21)

3-methyl-4-[2-(N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino)-5-trifluoromethylphenoxymethyl]cinnamic acid

[0128]



TLC : Rf 0.42 (chloroform : methanol = 9:1);

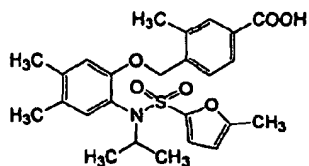
NMR(DMSO- $d_6$ ) :  $\delta$  12.36 (br s, 1H), 7.61-7.52 (m, 5H), 7.38 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 3.5 Hz, 1H), 6.54 (d, J = 16.0 Hz, 1H), 6.28 (d, J = 3.5 Hz, 1H), 5.24 (d, J = 13.0 Hz, 1H), 5.18 (d, J = 13.0 Hz, 1H), 4.26 (septet, J = 6.5 Hz, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 0.97 (d, J = 6.5 Hz, 6H).

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Example 2(22)

3-methyl-4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]benzoic acid

[0129]

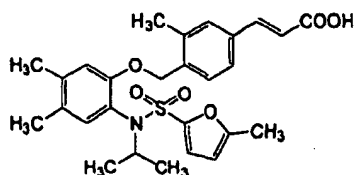


TLC : Rf 0.28 (n-hexane : ethyl acetate = 1 : 1);  
NMR :  $\delta$  7.97 (d, J = 7.8 Hz, 1H), 7.93 (s, 1H), 7.65 (d, J = 7.8 Hz, 1H), 6.82 (s, 1H), 6.79 (d, J = 3.3 Hz, 1H), 6.77 (s, 1H), 6.01 (dd, J = 3.3, 1.2 Hz, 1H), 5.08 (d, J = 13.2 Hz, 1H), 5.02 (d, J = 13.2 Hz, 1H), 4.47 (quint, J = 6.6 Hz, 1H), 2.40 (s, 3H), 2.29 (s, 3H), 2.25 (s, 3H), 2.17 (s, 3H), 1.11 (d, J = 6.6 Hz, 6H).

Example 2(23)

3-methyl-4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]cinnamic acid

[0130]

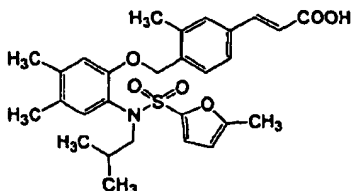


TLC : Rf 0.30 (n-hexane : ethyl acetate = 1 : 2);  
MS (FAB, Pos.) : 498 (M + H)<sup>+</sup>.

Example 2(24)

3-methyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]cinnamic acid

[0131]

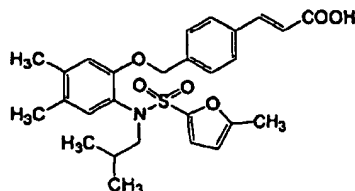


TLC : Rf 0.26 (n-hexane : ethyl acetate = 1 : 2);  
MS (FAB, Pos.) : 512 (M + H)<sup>+</sup>.

## Example 2(25)

4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]cinnamic acid

[0132]

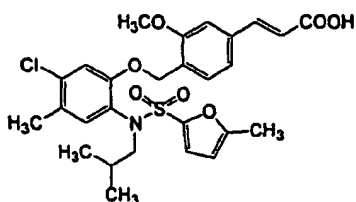


TLC : Rf 0.47 (chloroform : methanol = 9 : 1);  
 NMR(DMSO- $d_6$ ) :  $\delta$  7.69 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 16.2 Hz, 1H), 7.34 (d, J = 8.1 Hz, 2H), 6.93 (s, 1H), 6.90 (s, 1H), 6.79 (d, J = 3.3 Hz, 1H), 6.54 (d, J = 16.2 Hz, 1H), 6.13 (m, 1H), 5.10-4.80 (m, 2H), 3.40-3.20 (m, 2H, covered with H<sub>2</sub>O in DMSO- $d_6$ ), 2.18 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H), 1.58-1.42 (m, 1H), 0.82 (d, J = 6.6 Hz, 6H).

## Example 2(26)

3-methoxy-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4-methyl-5-chlorophenoxy]methyl]cinnamic acid

[0133]

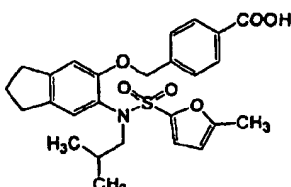


TLC : Rf 0.30 (chloroform : methanol = 9:1);  
 NMR :  $\delta$  7.76 (d, J = 15.9 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.26 (s, 1H), 7.20 (d, J = 8.1 Hz, 1H), 7.04 (s, 1H), 6.96 (s, 1H), 6.72 (d, J = 3.3 Hz, 1H), 6.46 (d, J = 15.9 Hz, 1H), 6.00-5.90 (m, 1H), 4.95 (brs, 2H), 3.91 (s, 3H), 3.48 (brs, 2H), 2.29 (s, 3H), 2.13 (s, 3H), 1.75-1.60 (m, 1H), 0.91 (brd, J = 6.6 Hz, 6H).

## Example 2(27)

4-[6-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl]benzoic acid

[0134]



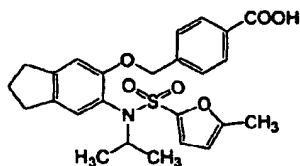
TLC : Rf 0.45 (chloroform : methanol = 9 : 1);  
 NMR :  $\delta$  8.11 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 7.12 (s, 1H), 6.77 (s, 1H), 6.73 (d, J = 3.3 Hz, 1H), 5.94 (m, 1H), 5.15-4.85 (br, 2H), 3.60-3.40 (br, 2H), 2.86 (t, J = 7.2 Hz, 4H), 2.14 (s, 3H), 2.13-2.00 (m, 2H), 1.68 (m, 1H),

1.02-0.82 (br, 6H).

Example 2(28)

4-[6-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxymethyl]benzoic acid

[0135]



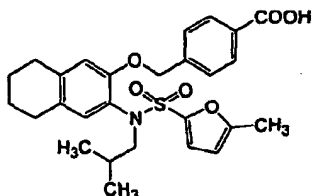
TLC : Rf 0.45 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  8.12 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 6.90 (s, 1H), 6.83 (s, 1H), 6.81 (d, J = 3.3 Hz, 1H), 6.02 (m, 1H), 5.17-5.05 (m, 2H), 4.49 (m, 1H), 2.93-2.79 (m, 4H), 2.31 (s, 3H), 2.15-2.00 (m, 2H), 1.12 (d, J = 6.6 Hz, 3H), 1.11 (d, J = 6.6 Hz, 3H).

Example 2(29)

4-[7-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-1,2,3,4-tetrahydronaphthalen-6-yloxymethyl]benzoic acid

[0136]



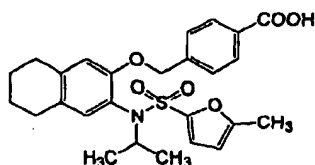
TLC : Rf 0.45 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  8.10 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H), 6.95 (s, 1H), 6.73 (d, J = 3.3 Hz, 1H), 6.57 (s, 1H), 5.93 (m, 1H), 5.15-4.82 (br, 2H), 3.48 (d, J = 7.2 Hz, 2H), 2.77-2.60 (m, 4H), 2.13 (s, 3H), 1.82-1.60 (m, 5H), 0.92 (d, J = 6.6 Hz, 6H).

Example 2(30)

4-[7-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-1,2,3,4-tetrahydronaphthalen-6-yloxymethyl]benzoic acid

[0137]



TLC : Rf 0.45 (chloroform : methanol = 9 : 1);

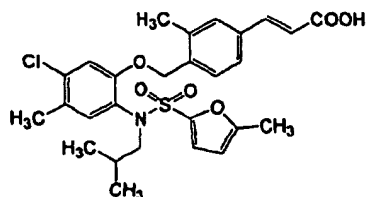
NMR :  $\delta$  8.12 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 3.3 Hz, 1H), 6.74 (s, 1H), 6.64 (s, 1H), 6.02 (m, 1H), 5.16-5.04 (m, 2H), 4.48 (m, 1H), 2.77-2.58 (m, 4H), 2.30 (s, 3H), 1.82-1.69 (m, 4H), 1.12 (d, J = 6.6 Hz, 3H), 1.11

(d, J = 6.6 Hz, 3H).

Example 2(31)

3-methyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4-methyl-5-chlorophenoxymethyl]cinnamic acid

[0138]



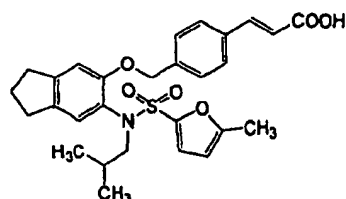
TLC : Rf 0.30 (chloroform : methanol = 9 : 1);

NMR(CD<sub>3</sub>OD) :  $\delta$  7.65 (d, J = 15.9 Hz, 1H), 7.46 (s) and 7.44 (d, J = 7.8 Hz) total 2H, 7.34 (d, J = 7.8 Hz, 1H), 7.18 (s, 1H), 7.14 (s, 1H), 6.71 (d, J = 3.3 Hz, 1H), 6.50 (d, J = 15.9 Hz, 1H), 6.07 (dd, J = 3.3, 0.9 Hz, 1H), 4.95 (m, 2H), 3.44 (d, J = 7.5 Hz, 2H), 2.35 (s, 3H), 2.28 (s, 3H), 2.09 (s, 3H), 1.61 (m, 1H), 0.87 (d, J = 6.6 Hz, 6H).

Example 2(32)

4-[6-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxymethyl]cinnamic acid

[0139]



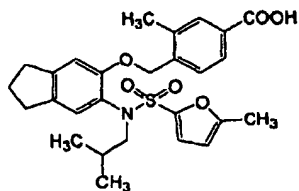
TLC : Rf 0.42 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.79 (d, J = 15.9 Hz, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.11 (s, 1H), 6.78 (s, 1H), 6.71 (d, J = 3.3 Hz, 1H), 6.47 (d, J = 15.9 Hz, 1H), 5.93 (m, 1H), 5.10-4.80 (br, 2H), 3.60-3.40 (br, 2H), 2.86 (t, J = 7.5 Hz, 4H), 2.14 (s, 3H), 2.08 (m, 2H), 1.68 (m, 1H), 1.00-0.82 (br, 6H).

Example 2(33)

3-methyl-4-[6-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxymethyl] benzoic acid

[0140]



TLC : Rf 0.33 (chloroform : methanol = 10 : 1);

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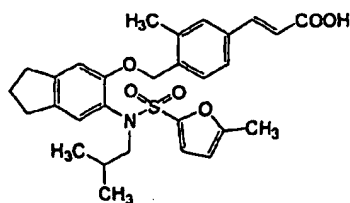
NMR(CDCl<sub>3</sub> + 1 drop of CD<sub>3</sub>OD) : δ 7.89 (d, J = 8.4 Hz, 1H), 7.88 (s, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.12 (s, 1H), 6.79 (s, 1H), 6.71 (d, J = 3.3 Hz, 1H), 5.94 (m, 1H), 5.06-4.74 (m, 2H), 3.60-3.37 (m, 2H), 2.92-2.82 (m, 4H), 2.34 (s, 3H), 2.17-2.03 (m, 2H), 2.10 (s, 3H), 1.69 (m, 1H), 1.01-0.80 (m, 6H).

## 5 Example 2(34)

3-methyl-4-[6-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxymethyl] cinnamic acid

[0141]

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20 TLC : Rf 0.30 chloroform : methanol = 10 : 1);

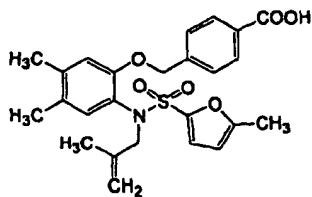
NMR : δ 7.78 (d, J = 15.9 Hz, 1H), 7.42-7.36 (m, 3H), 7.10 (s, 1H), 6.80 (s, 1H), 6.72 (d, J = 3.3 Hz, 1H), 6.46 (d, J = 15.9 Hz, 1H), 5.94 (m, 1H), 5.04-4.77 (m, 2H), 3.59-3.37 (m, 2H), 2.91-2.82 (m, 4H), 2.34 (s, 3H), 2.14-2.05 (m, 2H), 2.12 (s, 3H), 1.68 (m, 1H), 1.00-0.82 (m, 6H).

## 25 Example 2(35)

4-[2-[N-(2-methyl-2-propenyl)-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy]benzoic acid

[0142]

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40 TLC : Rf 0.42(chloroform : methanol = 10 : 1);

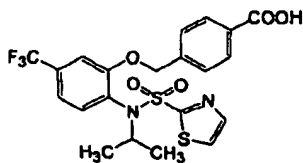
NMR : δ 8.11 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H), 7.02 (s, 1H), 6.74 (d, J = 3.3 Hz, 1H), 6.67 (s, 1H), 6.00-5.95 (m, 1H), 5.00 (brs, 2H), 4.77 (s, 2H), 4.26 (brs, 2H), 2.21 (s, 3H), 2.17 (s, 3H), 2.13 (s, 3H), 1.78 (s, 3H).

## 45 Example 2(36)

4-[2-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy]benzoic acid

[0143]

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TLC : Rf 0.58 (ethyl acetate);

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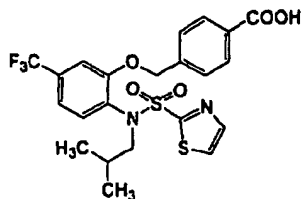
NMR(CD<sub>3</sub>OD) :  $\delta$  8.03 (d, J = 8.7 Hz, 2H), 7.92 (d, J = 3.3 Hz, 1H), 7.82 (d, J = 3.3 Hz, 1H), 7.54 (d, J = 8.4 Hz, 2H), 7.43 (brs, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.30 (brd, J = 8.1 Hz, 1H), 5.23 (ABd, J = 12.6 Hz) and 5.14 (ABd, J = 12.6 Hz) total 2H, 4.64 (sept, J = 6.9 Hz, 1H), 1.15 (d, J = 6.9 Hz) and 1.14 (d, J = 6.9 Hz) total 6H.

## 5 Example 2(37)

4-[2-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy]benzoic acid

[0144]

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TLC : Rf 0.60 (ethyl acetate);

NMR(CD<sub>3</sub>OD) :  $\delta$  8.02 (d, J = 8.7 Hz, 2H), 7.74 (m, 2H), 7.52 (d, J = 7.2 Hz, 1H), 7.38 (d, J = 8.7 Hz) and 7.37 (s) total 3H, 7.32 (brd, J = 7.2 Hz, 1H), 5.02 (br, 2H), 3.60 (brd, J = 7.5 Hz, 2H), 1.70-1.58 (m, 1H), 0.92 (d, J = 6.9 Hz, 6H).

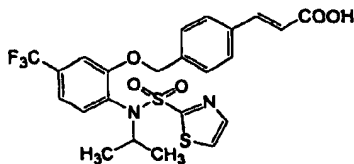
25

## Example 2(38)

4-[2-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy] cinnamic acid

[0145]

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TLC : Rf 0.42 (chloroform : methanol = 9 : 1);

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NMR(CD<sub>3</sub>OD) :  $\delta$  7.91 (d, J = 3 Hz, 1H), 7.81 (d, J = 3 Hz, 1H), 7.69 (d, J = 15.9 Hz, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.42 (s, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.29 (brd, J = 8.1 Hz, 1H), 6.52 (d, J = 15.9 Hz, 1H), 5.18 (ABd, J = 12.3 Hz) and 5.09 (ABd, J = 12.3 Hz) total 2H, 4.63 (sept, J = 6.6 Hz, 1H), 1.15 (d, J = 6.6 Hz) and 1.13 (d, J = 6.6 Hz) total 6H.

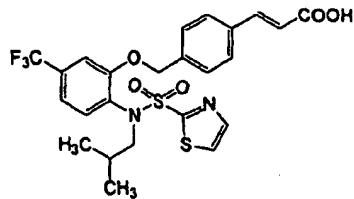
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## Example 2(39)

4-[2-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy]cinnamic acid

[0146]

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TLC: Rf 0.42 (chloroform: methanol = 9 : 1);

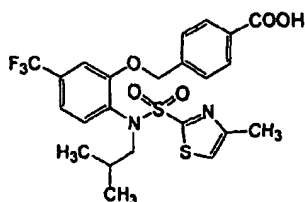
NMR(CD<sub>3</sub>OD) :  $\delta$  7.76-7.70 (m, 2H), 7.64 (s) and 7.63 (d, J = 15.9 Hz) total 3H, 7.52 (d, J = 8.1 Hz, 1H), 7.38-7.28 (m, 4H), 6.53 (d, J = 15.9 Hz, 1H), 5.04-4.90 (m, 2H), 3.60 (brd, J = 6.9 Hz, 2H), 1.72-1.56 (m, 1H), 0.92 (d, J = 6.6 Hz, 6H).

## 5 Example 2(40)

4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy] benzoic acid

[0147]

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20 TLC : Rf 0.42 (chloroform : methanol = 9 : 1);

NMR(CD<sub>3</sub>OD) :  $\delta$  8.03 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.1 Hz, 1H), 7.42-7.30 (m) and 7.27 (s) total 5H, 5.18-4.90 (m, 2H), 3.63-3.58 (m, 2H), 2.23 (d, J = 0.9 Hz, 3H), 1.66 (m, 1H), 0.93 (d, J = 6.6 Hz, 6H).

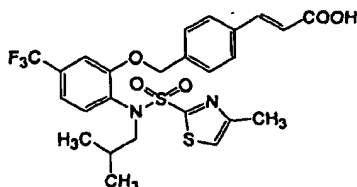
## 25 Example 2(41)

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4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy] cinnamic acid

[0148]

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TLC : Rf 0.32 (chloroform : methanol = 9 : 1);

NMR(DMSO-d<sub>6</sub>) :  $\delta$  7.70 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 15.9 Hz, 1H), 7.56-7.46 (m, 3H), 7.38 (d, J = 8.7 Hz, 1H), 7.29 (d, J = 8.1 Hz, 2H), 6.56 (d, J = 15.9 Hz, 1H), 5.20-4.85 (m, 2H), 3.49 (d, J = 6.9 Hz, 2H), 2.21 (s, 3H), 1.53 (m, 1H), 0.84 (d, J = 6.6 Hz, 6H).

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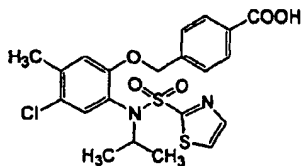
## Example 2(42)

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4-[2-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]-4-chloro-5-methylphenoxy]benzoic acid

[0149]

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TLC : Rf 0.39 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  8.13 (d, J = 8.1 Hz, 2H), 7.91 (d, J = 3.0 Hz, 1H), 7.52 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 3.0 Hz, 1H), 7.10 (s,

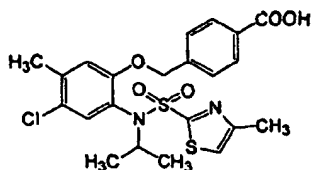
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1H), 6.85 (s, 1H), 5.09 (s, 2H), 4.67 (m, 1H), 2.36 (s, 3H), 1.16 (d, J = 6.6 Hz, 3H), 1.15 (d, J = 6.6 Hz, 3H).

## Example 2(43)

4-[2-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-chloro-5-methylphenoxy]benzoic acid

[0150]



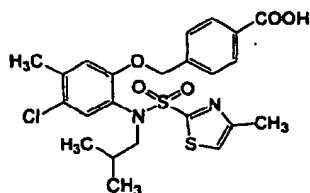
TLC : Rf 0.39 (chloroform methanol = 10 : 1);

NMR :  $\delta$  8.13 (d, J = 8.1 Hz, 2H), 7.52 (d, J = 8.1 Hz, 2H), 7.09 (s, 1H), 7.04 (m, 1H), 6.85 (s, 1H), 5.10 (s, 2H), 4.68 (m, 1H), 2.49 (d, J = 0.6 Hz, 3H), 2.36 (s, 3H), 1.15 (d, J = 6.6 Hz, 3H), 1.14 (d, J = 6.6 Hz, 3H).

## Example 2(44)

4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-chloro-5-methylphenoxy]benzoic acid

[0151]



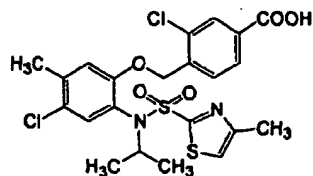
TLC : Rf 0.40 (chloroform : methanol = 10 : 1);

NMR :  $\delta$  8.12 (d, J = 7.5 Hz, 2H), 7.37 (d, J = 7.5 Hz, 2H), 7.27 (d, J = 1.2 Hz, 1H), 6.96 (m, 1H), 6.78 (s, 1H), 5.10-4.78 (m, 2H), 3.57 (brs, 2H), 2.35 (s, 3H), 2.34 (s, 3H), 1.70 (m, 1H), 0.94 (d, J = 6.6 Hz, 6H).

## Example 2(45)

3-chloro-4-[2-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-chloro-5-methylphenoxy]benzoic acid

[0152]



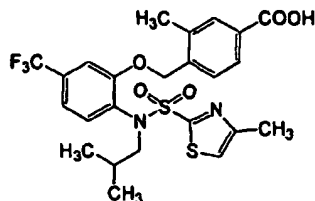
TLC: Rf 0.69 (chloroform: methanol: water = 8 : 2 : 0.2);

NMR :  $\delta$  8.12 (d, J = 1.5 Hz, 1H), 8.06 (dd, J = 8.1, 1.5 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.11-7.10 (m, 2H), 6.86 (s, 1H), 5.23 (d, J = 14.4 Hz, 1H), 5.15 (d, J = 14.4 Hz, 1H), 4.71 (quint, J = 6.6 Hz, 1H), 2.52 (d, J = 1.2 Hz, 3H), 2.38 (s, 3H), 1.56 (d, J = 6.6 Hz, 3H), 1.34 (d, J = 6.6 Hz, 3H).

Example 2(46)

3-methyl-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl]benzoic acid

[0153]



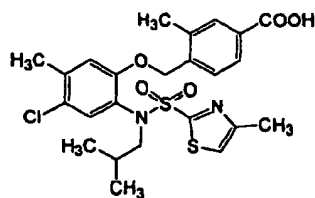
TLC : Rf 0.44 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.96 (d, J = 8.4 Hz, 1H), 7.95 (s, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.32-7.24 (m, 1H), 7.20 (s, 1H), 6.98 (s, 1H), 5.06-4.85 (m, 2H), 3.70-3.50 (m, 2H), 2.39 (s, 3H), 2.34 (s, 3H), 1.75-1.59 (m, 1H), 0.91 (d, J = 6.6 Hz, 6H).

Example 2(47)

3-methyl-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-chloro-5-methylphenoxy]methyl]benzoic acid

[0154]



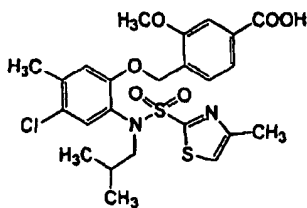
TLC : Rf 0.44 (chloroform : methanol = 9 : 1);

NMR(DMSO- $d_6$ ) :  $\delta$  7.79 (s, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.56 (s, 1H), 7.29 (s, 1H), 7.27 (d, J = 8.1 Hz, 1H), 7.23 (s, 1H), 5.20-4.65 (m, 2H), 3.55-3.35 (m, 2H), 2.36 (s, 3H), 2.31 (s, 3H), 2.21 (s, 3H), 1.65-1.47 (m, 1H), 0.84 (d, J = 6.6 Hz, 6H).

Example 2(48)

3-methoxy-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-chloro-5-methylphenoxy]methyl]benzoic acid

[0155]



TLC Rf 0.48 (chloroform : methanol = 9 : 1);

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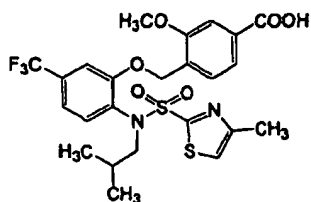
NMR :  $\delta$  7.74 (dd, J = 7.8, 1.2 Hz, 1H), 7.59 (d, J = 1.2 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.30 (s, 1H), 6.94 (s, 1H), 6.81 (s, 1H), 5.10-4.70 (m, 2H), 3.94 (s, 3H), 3.59 (br, 2H), 2.35 (s, 3H), 2.34 (s, 3H), 1.80-1.60 (m, 1H), 1.12 (d, J = 6.9 Hz, 6H).

5 Example 2(49)

3-methoxy-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy]benzoic acid

[0156]

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20 TLC: Rf 0.40 (chloroform : methanol = 9 : 1);

NMR:  $\delta$  7.73 (dd, J = 8.1, 1.5 Hz, 1H), 7.60 (d, J = 1.5 Hz, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.34-7.19 (m, 3H), 6.95 (m, 1H), 5.12-4.80 (m, 2H), 3.95 (s, 3H), 3.77-3.48 (m, 2H), 2.34 (s, 3H), 1.77-1.60 (m, 1H), 0.94 (d, J = 6.6 Hz, 6H).

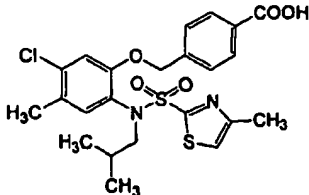
25 Example 2(50)

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4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-methyl-5-chlorophenoxy]benzoic acid

[0157]

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TLC: Rf 0.38 (chloroform: methanol = 9 : 1);

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NMR :  $\delta$  8.11 and 7.33 (each d, J = 8.4 Hz, each 2H), 7.22 (s, 1H), 6.92 and 6.91 (each s, each 1H), 5.10-4.70 (m, 2H), 3.74-3.42 (m, 2H), 2.31 and 2.30 (each s, each 3H), 1.78-1.62 (m, 1H), 1.05-0.83 (m, 6H).

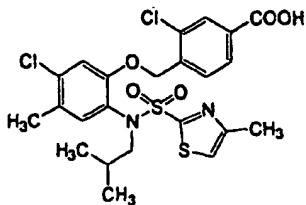
Example 2(51)

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3-chloro-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-methyl-5-chlorophenoxy]benzoic acid

[0158]

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TLC : Rf 0.28 (chloroform : methanol = 9 : 1);

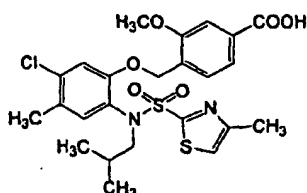
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NMR :  $\delta$  8.11 (s, 1H), 8.02 and 7.45 (each d, J = 8.1 Hz, each 1H), 7.21 (s, 1H), 6.97 (s, 1H), 6.94 (s, 1H), 5.12-4.74 (m, 2H), 3.75-3.45 (m, 2H), 2.32 and 2.31 (each s, each 3H), 1.80-1.62 (m, 1H), 1.05-0.82 (m, 6H).

Example 2(52)

3-methoxy-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-methyl-5-chlorophenoxymethyl]benzoic acid

[0159]



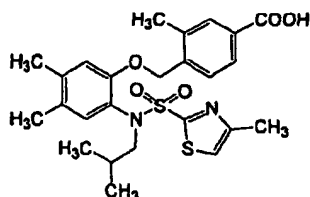
TLC: Rf 0.35 (chloroform: methanol = 9 : 1);

NMR :  $\delta$  7.73 (d, J = 7.8 Hz, 1H), 7.59 (s, 1H), 7.30-7.20 (m, 2H), 6.95 (s, 1H), 6.91 (s, 1H), 5.09-4.62 (m, 2H), 3.94 (s, 3H), 3.78-3.45 (m, 2H), 2.31 (s, 6H), 1.79-1.63 (m, 1H), 1.08-0.85 (m, 6H).

Example 2(53)

3-methyl-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxymethyl]benzoic acid

[0160]



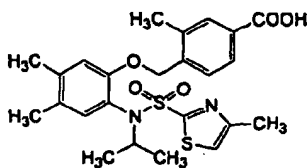
TLC : Rf 0.76 (chloroform : methanol : water = 8 : 2 : 0.2);

NMR :  $\delta$  7.93 (d, J = 8.1 Hz, 1H), 7.92 (s, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.08 (s, 1H), 6.90 (d, J = 0.9 Hz, 1H), 6.71 (s, 1H), 4.91 (br, 1H), 4.79 (br, 1H), 3.65 (br, 1H), 3.56 (br, 1H), 2.35 (s, 3H), 2.30 (d, J = 0.9 Hz, 3H), 2.24 (s, 3H), 2.19 (s, 3H), 1.71 (sep, J = 6.9 Hz, 1H), 1.03-0.92 (br, 6H).

Example 2(54)

3-methyl-4-[2-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxymethyl]benzoic acid

[0161]



TLC: Rf 0.78 (chloroform: methanol: water = 8 : 2:0.2);

NMR :  $\delta$  7.95 (d, J = 8.1 Hz, 1H), 7.93 (s, 1H), 7.54 (d, J = 8.1 Hz, 1H), 6.98 (d, J = 0.9 Hz, 1H), 6.86 (s, 1H), 6.78 (s,

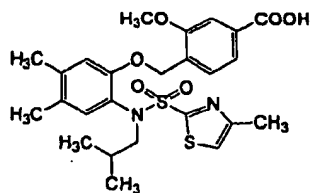
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1H), 5.03 (d, J = 13.2 Hz, 1H), 4.98 (d, J = 13.2 Hz, 1H), 4.69 (quint, J = 6.6 Hz, 1H), 2.46 (d, J = 0.9 Hz, 3H), 2.39 (s, 3H), 2.25 (s, 3H), 2.16 (s, 3H), 1.17 (d, J = 6.6 Hz, 3H), 1.13 (d, J = 6.6 Hz, 3H).

## Example 2(55)

3-methoxy-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxy]benzoic acid

[0162]



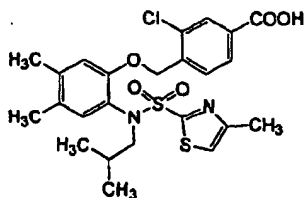
TLC: Rf 0.89 (chloroform: methanol = 9 : 1);

NMR:  $\delta$  7.72 (dd, J = 8.1, 1.2 Hz, 1H), 7.57 (d, J = 1.2 Hz, 1H), 7.26 (d, J = 8.1 Hz, 1H), 7.11 (s, 1H), 6.87 (s, 1H), 6.71 (s, 1H), 4.95 (br, 1H), 4.75 (br, 1H), 3.93 (s, 3H), 3.69 (br, 1H), 3.56 (br, 1H), 2.29 (s, 3H), 2.23 (s, 3H), 2.19 (s, 3H), 1.80-1.65 (m, 1H), 0.97 (br, 6H).

## Example 2(56)

3-chloro-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxy]benzoic acid

[0163]



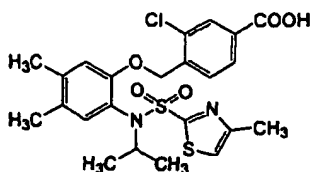
TLC : Rf 0.36 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  8.11 (d, J = 1.8 Hz, 1H), 8.01 (dd, J = 8.1, 1.8 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.08 (s, 1H), 6.95 (d, J = 0.6 Hz, 1H), 6.69 (s, 1H), 5.20-4.70 (br, 2H), 3.80-3.45 (br, 2H), 2.32 (d, J = 0.6 Hz, 3H), 2.24 (s, 3H), 2.19 (s, 3H), 1.75 (m, 1H), 1.07-0.85 (br, 6H).

## Example 2(57)

3-chloro-4-[2-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxy]benzoic acid

[0164]



TLC : Rf 0.36 (chloroform : methanol = 9 : 1);

NMR(CDCl<sub>3</sub> + CD<sub>3</sub>OD) :  $\delta$  8.06 (d, J = 1.8 Hz, 1H), 7.98 (dd, J = 8.1, 1.8 Hz, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.05 (d, J = 0.6 Hz, 1H), 6.86 (s, 1H), 6.76 (s, 1H), 5.14 (d, J = 14.1 Hz, 1H), 5.08 (d, J = 14.1 Hz, 1H), 4.70 (m, 1H), 2.47 (d, J

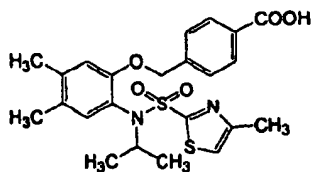
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= 0.6 Hz, 3H), 2.25 (s, 3H), 2.17 (s, 3H), 1.17 (d, J = 6.6 Hz, 3H), 1.15 (d, J = 6.6 Hz, 3H).

## Example 2(58)

4-[2-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxyethyl]benzoic acid

[0165]



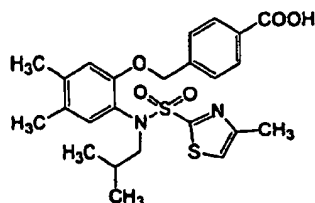
TLC: Rf 0.45 (chloroform : methanol = 10 : 1);

NMR:  $\delta$  8.11-8.08 (m, 2H), 7.49 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 0.9 Hz, 1H), 6.86 (s, 1H), 6.75 (s, 1H), 5.06 (d, J = 12.9 Hz, 1H), 5.04 (d, J = 12.9 Hz, 1H), 4.71 (m, 1H), 2.46 (d, J = 0.9 Hz, 3H), 2.23 (s, 3H), 2.16 (s, 3H), 1.18 (d, J = 6.6 Hz, 3H), 1.15 (d, J = 6.6 Hz, 3H).

## Example 2(59)

4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxyethyl] benzoic acid

[0166]



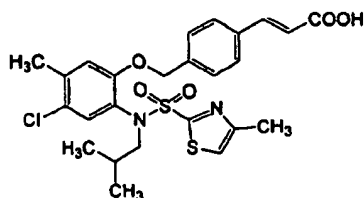
TLC: Rf 0.43 (chloroform : methanol = 10 : 1);

NMR:  $\delta$  8.09 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.08 (s, 1H), 6.89 (d, J = 0.9 Hz, 1H), 6.68 (s, 1H), 5.08-4.68 (m, 2H), 3.75-3.45 (m, 2H), 2.30 (s, 3H), 2.23 (s, 3H), 2.18 (s, 3H), 1.71 (m, 1H), 1.04-0.83 (m, 6H).

## Example 2(60)

4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-chloro-5-methylphenoxyethyl]cinnamic acid

[0167]



TLC: Rf 0.22 (chloroform : methanol = 9 : 1);

NMR(CD<sub>3</sub>OD):  $\delta$  7.69 (d, J = 16.2 Hz, 1H), 7.61 (d, J = 8.1 Hz, 2H), 7.32-7.24 (m) and 7.29 (d, J = 8.1 Hz) total 4H, 7.05 (s, 1H), 6.52 (d, J = 16.2 Hz, 1H), 5.05-4.70 (m, 2H, covered with H<sub>2</sub>O in CD<sub>3</sub>OD), 3.63-3.50 (m, 2H), 2.37 (s,

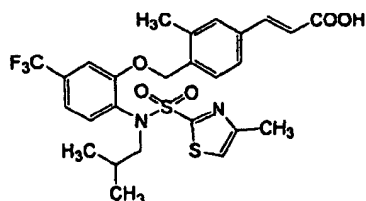
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3H), 2.22 (d, J = 0.9 Hz, 3H), 1.65 (m, 1H), 0.93 (d, J = 6.3 Hz, 6H).

Example 2(61)

3-methyl-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl]cinnamic acid

[0168]



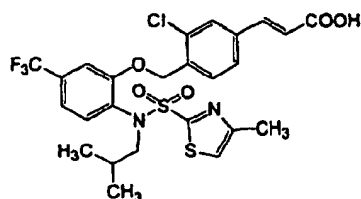
TLC : Rf 0.37 (chloroform : methanol = 9:1);

NMR :  $\delta$  7.76 (d, J = 16.2 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.45-7.35 (m, 2H), 7.32-7.23 (m, 2H), 7.20 (m, 1H), 6.98 (s, 1H), 6.48 (d, J = 16.2 Hz, 1H), 5.03-4.82 (m, 2H), 3.70-3.50 (m, 2H), 2.36 (s, 3H), 2.34 (s, 3H), 1.74-1.58 (m, 1H), 0.91 (d, J = 6.9 Hz, 6H).

Example 2(62)

3-chloro-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl]cinnamic acid

[0169]



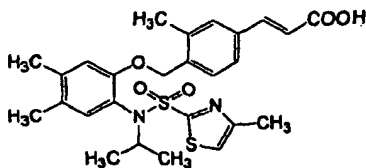
TLC : Rf 0.28 (n-hexane : ethyl acetate = 1 : 2);

NMR :  $\delta$  7.71 (d, J = 16.2 Hz, 1H), 7.58 (s, 1H), 7.52-7.44 (m, 3H), 7.29 (d, J = 8.1 Hz, 1H), 7.19 (s, 1H), 7.01 (d, J = 0.9 Hz, 1H), 6.50 (d, J = 16.2 Hz, 1H), 5.02 (br, 2H), 3.62 (d, J = 6.6 Hz, 2H), 2.35 (s, 3H), 1.68 (sep, J = 6.6 Hz, 1H), 0.93 (d, J = 6.6 Hz, 6H).

Example 2(63)

3-methyl-4-[2-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]cinnamic acid

[0170]



TLC : Rf 0.20 (n-hexane : ethyl acetate = 1 : 2);

MS (FAB, Pos.) : 515(M + H)<sup>+</sup>.

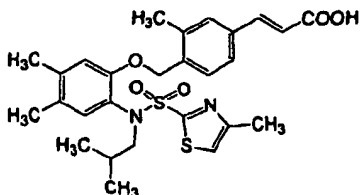


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Example 2(64)

3-methyl-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]cinnamic acid

[0171]

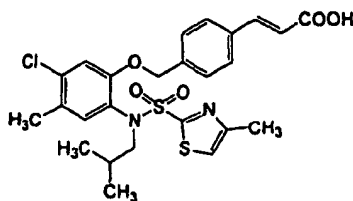


TLC: Rf 0.22 (n-hexane: ethyl acetate = 1 : 2);  
MS (FAB, Pos.): 529(M + H)<sup>+</sup>.

Example 2(65)

4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-methyl-5-chlorophenoxy]methyl]cinnamic acid

[0172]

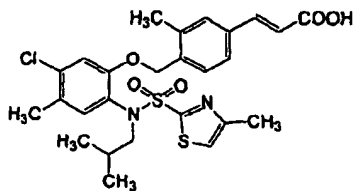


TLC: Rf 0.31 (chloroform: methanol = 9 : 1);  
NMR :  $\delta$  7.79 (d, J = 15.9 Hz, 1H), 7.56 and 7.27 (each d, J = 8.1 Hz, each 2H), 7.21 (s, 1H), 6.95-6.88 (m, 2H), 6.48 (d, J = 15.9 Hz, 1H), 5.00-4.65 (m, 2H), 3.72-3.42 (m, 2H), 2.33-2.22 (m, 6H), 1.78-1.60 (m, 1H), 1.05-0.83 (m, 6H).

Example 2(66)

3-methyl-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-methyl-5-chlorophenoxy]methyl]cinnamic acid

[0173]



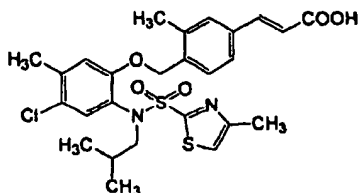
TLC : Rf 0.30 (chloroform : methanol = 9 : 1);  
NMR :  $\delta$  7.76 (d, J = 16.2 Hz, 1H), 7.42-7.37 (m, 2H), 7.30-7.15 (m, 2H), 6.98-6.89 (m, 2H), 6.47 (d, J = 16.2 Hz, 1H), 4.95-4.67 (m, 2H), 3.72-3.40 (m, 2H), 2.38-2.22 (m, 9H), 1.77-1.61 (m, 1H), 1.05-0.82 (m, 6H).

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## Example 2(67)

3-methyl-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-chloro-5-methylphenoxy]methyl]cinnamic acid

[0174]

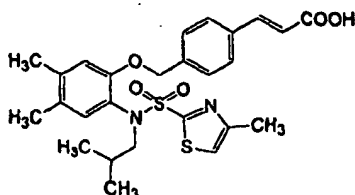


TLC : Rf 0.41 (chloroform : methanol = 9 : 1);  
NMR :  $\delta$  7.76 (d, J = 16.2 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.38 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.23 (s, 1H), 6.97 (s, 1H), 6.81 (s, 1H), 6.47 (d, J = 16.2 Hz, 1H), 5.04-4.66 (m, 2H), 3.65-3.39 (m, 2H), 2.36 (s, 3H), 2.35 (s, 3H), 2.33 (s, 3H), 1.75-1.61 (m, 1H), 0.92 (d, J = 6.6 Hz, 6H).

## Example 2(68)

4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]cinnamic acid

[0175]

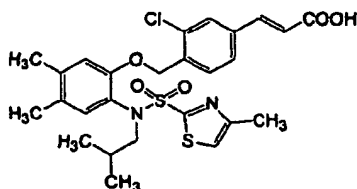


TLC : Rf 0.33 (chloroform : methanol = 10 : 1);  
MS (APCI, Neg. 20V) : 513 (M - H)<sup>-</sup>.

## Example 2(69)

3-chloro-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]cinnamic acid

[0176]



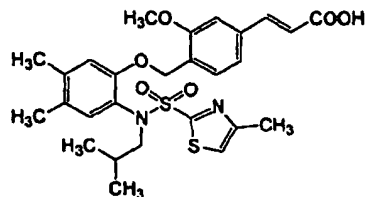
TLC : Rf 0.17 (chloroform : methanol = 9 : 1);  
NMR(CD<sub>3</sub>OD) :  $\delta$  7.69 (d, J = 1.8 Hz, 1H), 7.65 (d, J = 15.9 Hz, 1H), 7.59 (dd, J = 8.1, 1.5 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 1.2 Hz, 1H), 7.04 (s, 1H), 6.88 (s, 1H), 6.57 (d, J = 15.9 Hz, 1H), 5.10-4.60 (m, 2H), 3.63-3.50 (m, 2H), 2.28 (s, 3H), 2.21 (d, J = 1.2 Hz) and 2.20 (s) total 6H, 1.66 (m, 1H), 1.03-0.85 (m, 6H).

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## Example 2(70)

3-methoxy-4-[2-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]cinnamic acid

[0177]

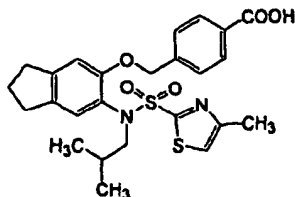


TLC : Rf 0.40 (dichloromethane : methanol = 10 : 1);  
MS (FAB, Pos.): 545 (M + H)<sup>+</sup>.

## Example 2(71)

4-[6-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]benzoic acid

[0178]

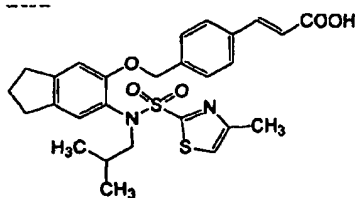


TLC : Rf 0.43 (chloroform : methanol = 9 : 1);  
NMR :  $\delta$  8.10 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.16 (s, 1H), 6.89 (d, J = 0.9 Hz, 1H), 6.76 (s, 1H), 5.06-4.70 (br, 2H), 3.78-3.45 (br, 2H), 2.87 (t, J = 7.5 Hz, 4H), 2.31 (d, J = 0.9 Hz, 3H), 2.09 (m, 2H), 1.74 (m, 1H), 1.04-0.86 (br, 6H).

## Example 2(72)

4-[6-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid

[0179]

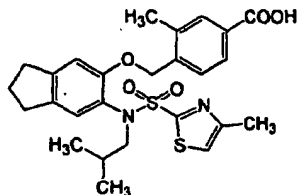


TLC: Rf 0.42 (chloroform: methanol = 9 : 1);  
NMR :  $\delta$  7.79 (d, J = 15.9 Hz, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.15 (s, 1H), 6.89 (d, J = 0.9 Hz, 1H), 6.77 (s, 1H), 6.47 (d, J = 15.9 Hz, 1H), 5.05-4.60 (br, 2H), 3.78-3.45 (br, 2H), 2.86 (t, J = 7.8 Hz, 4H), 2.30 (d, J = 0.9 Hz, 3H), 2.08 (m, 2H), 1.73 (m, 1H), 1.06-0.83 (br, 6H).

## Example 2(73)

3-methyl-4-[6-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl] benzoic acid

[0180]



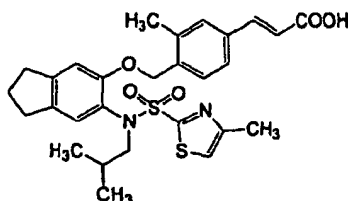
TLC : Rf 0.34 (dichloromethane : methanol = 19 : 1);

NMR :  $\delta$  7.95-7.92 (m, 2H), 7.31 (d, J = 7.8 Hz, 1H), 7.16 (s, 1H), 6.91 (brs, 1H), 6.79 (s, 1H), 4.93 (brs, 1H), 4.73 (brs, 1H), 3.75-3.45 (m, 2H), 2.92-2.84 (m, 4H), 2.34 (s, 3H), 2.31 (d, J = 0.6 Hz, 3H), 2.10 (m, 2H), 1.74 (m, 1H), 1.08-0.80 (brs, 6H).

## Example 2(74)

3-methyl-4-[6-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl] cinnamic acid

[0181]



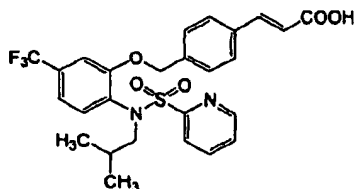
TLC : Rf 0.32 (dichloromethane : methanol = 19 : 1);

NMR :  $\delta$  7.76 (d, J = 15.9 Hz, 1H), 7.40-7.36 (m, 2H), 7.25 (m, 1H), 7.14 (s, 1H), 6.91 (brs, 1H), 6.80 (s, 1H), 6.46 (d, J = 15.9 Hz, 1H), 4.90 (brs, 1H), 4.69 (brs, 1H), 3.75-3.43 (m, 2H), 2.95-2.80 (m, 4H), 2.31 (s, 6H), 2.09 (m, 2H), 1.72 (m, 1H), 1.05-0.85 (brs, 6H).

## Example 2(75)

4-[2-[N-isobutyl-N-(2-pyridylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl]cinnamic acid

[0182]



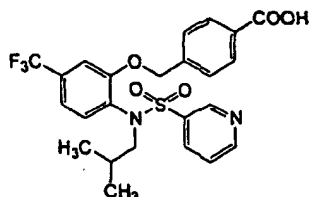
TLC : R.f 0.37 (chloroform : methanol = 9 : 1);

NMR(CD<sub>3</sub>OD) :  $\delta$  8.39 (ddd, J = 4.5, 1.5, 0.9 Hz, 1H), 7.82 (dt, J = 7.5, 1.5 Hz, 1H), 7.72-7.64 (m, 2H), 7.60 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 7.5 Hz, 1H), 7.38 (ddd, J = 7.5, 4.5, 0.9 Hz, 1H), 7.34-7.22 (m, 4H), 6.54 (d, J = 15.9 Hz, 1H), 4.95-4.78 (m, 2H), 3.61 (d, J = 6.6 Hz, 2H), 1.60 (m, 1H), 0.91 (d, J = 6.9 Hz, 6H).

Example 2(76)

4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-5-trifluoromethylphenoxy]benzoic acid

[0183]



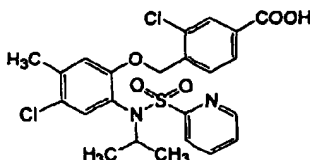
TLC: Rf 0.27 (chloroform: methanol = 9 : 1);

NMR(CD<sub>3</sub>OD) : δ 8.63 (m, 1H), 8.53 (dd, J = 5.1, 1.8 Hz, 1H), 7.99 (d, J = 8.4 Hz) and 7.94 (m) total 3H, 7.56 (d, J = 7.5 Hz, 1H), 7.40-7.29 (m, 3H), 7.23 (d, J = 8.4 Hz, 2H), 5.10-4.80 (m, 2H), 3.58-3.40 (m, 2H), 1.61 (m, 1H), 0.92 (brd, J = 6 Hz, 6H).

Example 2(77)

3-chloro-4-[2-[N-isopropyl-N-(2-pyridylsulfonyl)amino]-4-chloro-5-methylphenoxy] benzoic acid

[0184]



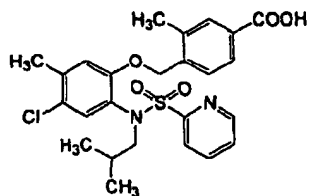
TLC : Rf 0.43 (chloroform : methanol = 9 : 1);

NMR(CD<sub>3</sub>OD) : δ 8.63 (m, 1H), 8.02 (d, J = 1.8 Hz, 1H), 7.98-7.84 (m, 3H), 7.70 (d, J = 8.1 Hz, 1H), 7.50 (m, 1H), 7.11 (s, 1H), 7.09 (s, 1H), 5.16 (ABd, J = 13.5 Hz) and 5.08 (ABd, J = 13.5 Hz) total 2H, 4.61 (sept, J = 6.6 Hz, 1H), 2.39 (3, 3H), 1.12 (d, J = 6.6 Hz) and 1.10 (d, J = 6.6 Hz) total 6H.

Example 2(78)

3-methyl-4-[2-[N-isobutyl-N-(2-pyridylsulfonyl)amino]-4-chloro-5-methylphenoxy] benzoic acid

[0185]



TLC : Rf 0.37 (chloroform: methanol = 10 : 1);

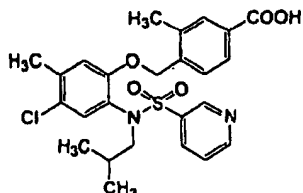
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NMR :  $\delta$  8.52 (m, 1H), 7.94-7.92 (m, 2H), 7.77-7.68 (m, 2H), 7.31-7.24 (m, 3H), 6.76 (s, 1H), 4.83 (brs, 2H), 3.65-3.50 (m, 2H), 2.34 (s, 6H), 1.66 (m, 1H), 0.91 (d, J = 6.6 Hz, 6H).

## Example 2(79)

3-methyl-4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4-chloro-5-methylphenoxy]benzoic acid

[0186]



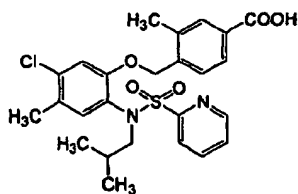
TLC : Rf 0.16 (dichloromethane : methanol = 20 : 1);

NMR :  $\delta$  12.90 (s, 1H), 8.67 (d, J = 1.8 Hz, 1H), 8.62 (dd, J = 4.8, 1.8 Hz, 1H), 7.94 (dt, J = 8.1, 1.8 Hz, 1H), 7.74 (s, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.37 (dd, J = 8.1, 4.8 Hz, 1H), 7.27 (s, 1H), 7.24 (s, 1H), 7.01 (d, J = 8.1 Hz, 1H), 4.95 (br, 1H), 4.76 (br, 1H), 3.45-3.30 (m, 2H), 2.34 (s, 3H), 2.24 (s, 3H), 1.49 (sept, J = 6.6 Hz, 1H), 0.90-0.70 (br, 6H).

## Example 2(80)

3-methyl-4-[2-[N-isobutyl-N-(2-pyridylsulfonyl)amino]-4-methyl-5-chlorophenoxy]benzoic acid

[0187]



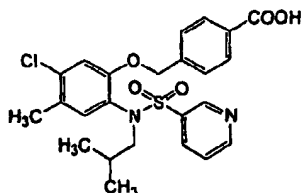
TLC : Rf 0.40 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  8.50-8.40 (m, 1H), 7.95-7.85 (m, 2H), 7.75-7.60 (m, 2H), 7.30-7.20 (m, 3H), 6.89 (s, 1H), 4.76 (br, 2H), 3.61 (br, 2H), 2.31 (s, 3H), 2.29 (s, 3H), 1.75-1.55 (m, 1H), 1.00-0.80 (m, 6H).

## Example 2(81)

4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4-methyl-5-chlorophenoxy]benzoic acid

[0188]



TLC : Rf 0.31 (chloroform : methanol = 9:1);

NMR :  $\delta$  8.83 (d, J = 2.4, 0.6 Hz, 1H), 8.61 (dd, J = 5.1, 1.8 Hz, 1H), 8.10 (d, J = 8.4 Hz, 2H), 7.78-7.71 (m, 1H), 7.36 (s, 1H), 7.29-7.22 (m, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.90 (s, 1H), 4.94-4.72 and 4.50-4.25 (each m, each 1H), 3.75-3.56

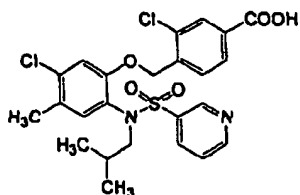
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and 3.45-3.24 (each m, each 1H), 2.36 (s, 3H), 1.79-1.63 (m, 1H), 1.16-0.80 (m, 6H).

## Example 2(82)

3-chloro-4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4-methyl-5-chlorophenoxymethyl] benzoic acid

[0189]



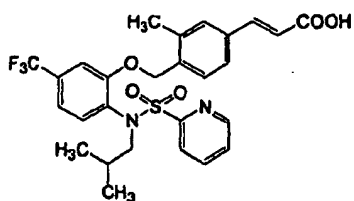
TLC: Rf 0.29 (chloroform: methanol =9 : 1);

NMR :  $\delta$  8.87 (d, J = 1.8 Hz, 1H), 8.63 (dd, J = 5.1, 1.8 Hz, 1H), 8.13 (d, J = 1.8 Hz, 1H), 8.03 (dd, J = 8.1, 1.8 Hz, 1H), 7.73-7.66 (m, 1H), 7.40 (s, 1H), 7.36 (dd, J = 8.1, 5.1 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 6.96 (s, 1H), 4.92-4.74 and 4.54-4.34 (each m, each 1H), 3.72-3.63 and 3.50-3.33 (each m, each 1H), 2.39 (s, 3H), 1.84-1.68 (m, 1H), 1.20-0.92 (m, 6H).

## Example 2(83)

3-methyl-4-[2-[N-isobutyl-N-(2-pyridylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl] cinnamic acid

[0190]



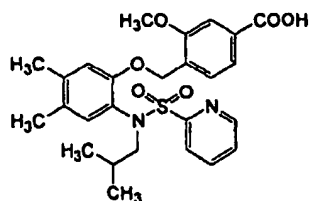
TLC: Rf 0.32 (chloroform : methanol =9 : 1);

NMR(DMSO- $d_6$ ):  $\delta$  12.39 (br s, 1H), 8.51 (d, J = 4.5 Hz, 1H), 7.90 (dd, J = 7.5, 7.5 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 16.0 Hz, 1H), 7.53-7.46 (m, 5H), 7.35 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 6.55 (d, J = 16.0 Hz, 1H), 5.00 (br s, 2H), 3.49 (d, J = 7.0 Hz, 2H), 2.25 (s, 3H), 1.45 (triple septet, J = 7.0, 7.0 Hz, 1H), 0.78 (d, J = 7.0 Hz, 6H).

## Example 2(84)

3-methoxy-4-[2-[N-isobutyl-N-(2-pyridylsulfonyl)amino]-4,5-dimethylphenoxy]methyl] benzoic acid

[0191]



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TLC: Rf 0.38 (chloroform: methanol = 9 : 1);

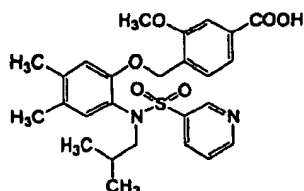
NMR :  $\delta$  8.47 (d, J = 4.8 Hz, 1H), 7.75-7.60 (m, 3H), 7.56 (d, J = 1.5 Hz, 1H), 7.20-7.15 (m, 2H), 7.12 (s, 1H), 6.65 (s, 1H), 4.84 (br, 1H), 4.66 (br, 1H), 3.92 (s, 3H), 3.61 (br, 2H), 2.22 (s, 3H), 2.18 (s, 3H), 1.80-1.60 (m, 1H), 0.96 (br, 6H).

## 5 Example 2(85)

3-methoxy-4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4,5-dimethylphenoxy]methyl benzoic acid

[0192]

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20 TLC : Rf 0.35 (chloroform : methanol = 9 : 1);

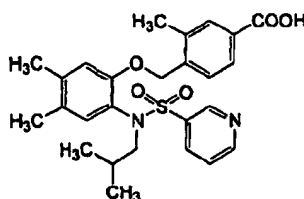
NMR :  $\delta$  8.86 (dd, J = 2.1, 0.9 Hz, 1H), 8.57 (dd, J = 5.1, 1.5 Hz, 1H), 7.75-7.65 (m, 2H), 7.61 (d, J = 1.5 Hz, 1H), 7.30-7.20 (m, 2H), 6.92 (d, J = 7.8 Hz, 1H), 6.72 (s, 1H), 4.75 (d, J = 12.3 Hz, 1H), 4.43 (d, J = 12.3 Hz, 1H), 3.93 (s, 3H), 3.75-3.60 (m, 1H), 3.45-3.35 (m, 1H), 2.29 (s, 3H), 2.25 (s, 3H), 1.85-1.65 (m, 1H), 1.09 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 6.3 Hz, 3H).

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## Example 2(86)

3-methyl-4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4,5-dimethylphenoxy]methyl benzoic acid

30 [0193]



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TLC : Rf 0.61 (chloroform : methanol : water = 8 : 2 : 0.2);

NMR(DMSO- $d_6$ ) :  $\delta$  12.87 (brs, 1H), 8.64 (d, J = 1.8 Hz, 1H), 8.59 (dd, J = 4.8, 1.8 Hz, 1H), 7.91 (dt, J = 8.1, 1.8 Hz, 1H), 7.73 (s, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.35 (dd, J = 8.1, 4.8 Hz, 1H), 7.04-6.96 (m, 3H), 4.92 (br, 1H), 4.66 (br, 1H), 3.48-3.22 (br, 2H), 2.23 (s, 3H), 2.22 (s, 3H), 2.15 (s, 3H), 1.49 (sep, J = 6.9 Hz, 1H), 0.98-0.75 (m, 6H).

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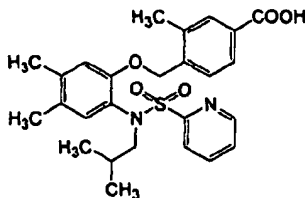
55



## Example 2(87)

3-methyl-4-[2-[N-isobutyl-N-(2-pyridylsulfonyl)amino]-4,5-dimethylphenoxy]methyl benzoic acid

[0194]



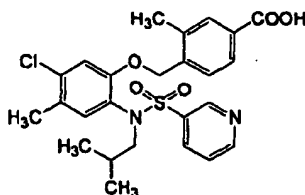
TLC : Rf 0.66 (chloroform : methanol: water = 8 : 2 : 0.2);

NMR(DMSO-d<sub>6</sub>) :  $\delta$  12.88 (s, 1H), 8.47 (d, J = 4.5 Hz, 1H), 7.87 (dt, J = 1.5, 7.8 Hz, 1H), 7.75 (s, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.42 (ddd, J = 7.8, 4.5, 1.5 Hz, 1H), 7.16 (d, J = 7.8 Hz, 1H), 6.93 (s, 1H), 6.91 (s, 1H), 4.80 (br, 2H), 3.57 (d, J = 6.6 Hz, 2H), 2.25 (s, 3H), 2.18 (s, 3H), 2.09 (s, 3H), 1.49 (sept, J = 6.6 Hz, 1H), 0.81 (d, J = 6.6 Hz, 6H).

## Example 2(88)

3-methyl-4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4-methyl-5-chlorophenoxy]methyl benzoic acid

[0195]



TLC : Rf 0.31 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  8.83 (d, J = 1.8 Hz, 1H), 8.61 (dd, J = 5.4, 1.8 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.92 (s, 1H), 7.78 (dt, J = 8.1, 1.8 Hz, 1H), 7.34 (s, 1H), 7.23 (dd, J = 8.1, 5.4 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.94 (s, 1H), 4.88-4.65 and 4.54-4.34 (each m, each 1H), 3.71-3.53 and 3.43-3.24 (each m, each 1H), 2.36 (s, 3H), 2.27 (s, 3H), 1.78-1.63 (m, 1H), 1.08-0.79 (m, 6H).

## Example 2(89)

4-[2-[N-isobutyl-N-(2-pyridylsulfonyl)amino]-4,5-dimethylphenoxy]methyl benzoic acid

[0196]



TLC : Rf 0.33 (chloroform : methanol = 10 : 1);

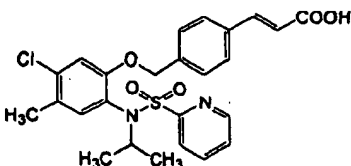
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NMR :  $\delta$  8.46 (m, 1H), 8.09-8.05 (m, 2H), 7.71-7.60 (m, 2H), 7.28-7.25 (m, 2H), 7.20 (m, 1H), 7.09 (s, 1H), 6.62 (s, 1H), 5.02-4.50 (m, 2H), 3.83-3.43 (m, 2H), 2.21 (s, 3H), 2.17 (s, 3H), 1.67 (m, 1H), 1.04-0.82 (m, 6H).

Example 2(90)

4-[2-[N-isopropyl-N-(2-pyridylsulfonyl)aminol-4-methyl-5-chlorophenoxymethyl]cinnamic acid

[0197]



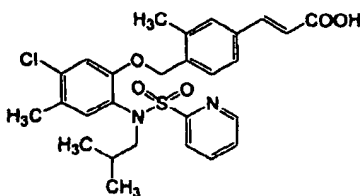
TLC : Rf 0.44 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  8.70-8.60 (m, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.79 (d, J = 15.9 Hz, 1H), 7.71 (dt, J = 1.8, 7.5 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.35-7.25 (m, 1H), 6.99 (s, 1H), 6.96 (s, 1H), 6.48 (d, J = 15.9 Hz, 1H), 4.96 (d, J = 12.3 Hz, 1H), 4.92 (d, J = 12.3 Hz, 1H), 4.75-4.60 (m, 1H), 2.26 (s, 3H), 1.14 (d, J = 6.9 Hz, 3H), 1.11 (d, J = 6.9 Hz, 3H).

Example 2(91)

3-methyl-4-[2-[N-isobutyl-N-(2-pyridylsulfonyl)amino]-4-methyl-5-chlorophenoxymethyl] cinnamic acid

[0198]



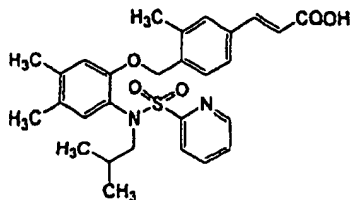
TLC : Rf 0.37 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  8.50-8.40 (m, 1H), 7.77 (d, J = 15.9 Hz, 1H), 7.75-7.60 (m, 2H), 7.40-7.36 (m, 2H), 7.25-7.20 (m, 2H), 7.15 (d, J = 8.4 Hz, 1H), 6.90 (s, 1H), 6.49 (d, J = 15.9 Hz, 1H), 4.73 (br, 2H), 3.60 (br, 2H), 2.29 (s, 3H), 2.28 (s, 3H), 1.70-1.55 (m, 1H), 0.91 (d, J = 6.6 Hz, 6H).

Example 2(92)

3-methyl-4-[2-[N-isobutyl-N-(2-pyridylsulfonyl)amino]-4,5-dimethylphenoxymethyl] cinnamic acid

[0199]



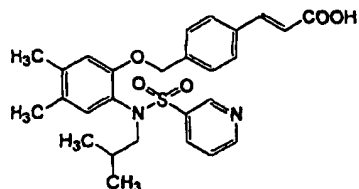
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TLC: Rf 0.36 (dichloromethane : methanol = 20 : 1);  
MS (FAB, Pos.): 509 (M + H)<sup>+</sup>.

## Example 2(93)

4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]cinnamic acid

[0200]

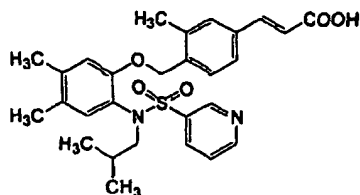


TLC : Rf 0.27 (chloroform : methanol = 10 : 1);  
MS(APCI, Neg. 20V) : 493 (M - H)<sup>-</sup>.

## Example 2(94)

3-methyl-4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]cinnamic acid

[0201]

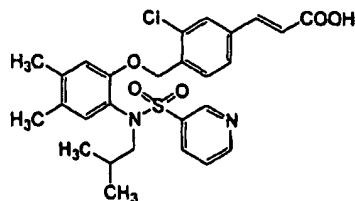


TLC: Rf 0.33 (dichloromethane: methanol = 20 : 1);  
MS(FAB, Pos.): 509 (M + H)<sup>+</sup>.

## Example 2(95)

3-chloro-4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]cinnamic acid

[0202]



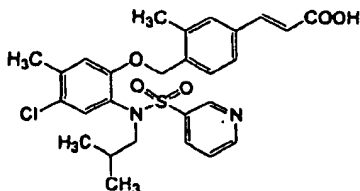
TLC : Rf 0.43 (chloroform : methanol = 3 : 1);

NMR :  $\delta$  8.88-8.82 (m, 1H), 8.61-8.52 (m, 1H), 7.75-7.68 (m, 1H), 7.61 (d, J = 15.9 Hz, 1H), 7.52 (d, J = 1.5 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.32-7.20 (m, 2H), 6.97 (d, J = 8.1 Hz, 1H), 6.70 (s, 1H), 6.50 (d, J = 15.9 Hz, 1H), 4.88-4.75 and 4.53-4.41 (each m, each 1H), 3.74-3.58 and 3.48-3.32 (each m, each 1H), 2.29 and 2.25 (each s, each 3H), 1.82-1.63 (m, 1H), 1.15-0.82 (m, 6H).

## Example 2(96)

3-methyl-4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-4-chloro-5-methylphenoxy]methyl] cinnamic acid

[0203]

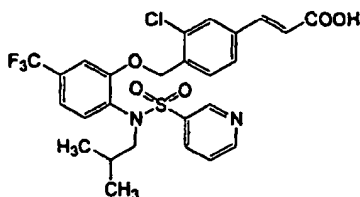


TLC : Rf 0.36 (chloroform : methanol = 9 : 1);  
 NMR(DMSO- $d_6$ ) :  $\delta$  8.65 (m, 2H), 7.94 (m, 1H), 7.54 (d, J = 16.2 Hz) and 7.51 (s) total 2H, 7.43 (d, J = 8.1 Hz, 1H), 7.38 (dd, J = 8.1, 4.8 Hz, 1H), 7.26 (s, 1H), 7.22 (s, 1H), 6.98 (d, J = 8.1 Hz, 1H), 6.53 (d, J = 16.2 Hz, 1H), 5.00-4.85 (m, 2H), 3.48-3.10 (m, 2H, covered with H<sub>2</sub>O in DMSO- $d_6$ ), 2.34 (s, 3H), 2.21 (s, 3H), 1.48 (m, 1H), 0.93 (m, 6H).

## Example 2(97)

3-chloro-4-[2-[N-isobutyl-N-(3-pyridylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl] cinnamic acid

[0204]

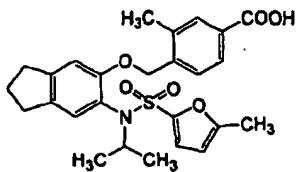


TLC : Rf 0.25 chloroform : methanol = 10 : 1);  
 MS (APCI, Neg. 20V) : 567 (M - H)<sup>-</sup>.

## Example 2(98)

3-methyl-4-[6-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl] benzoic acid

[0205]



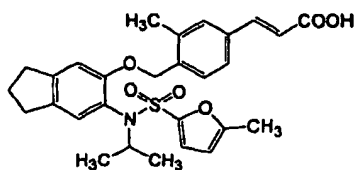
TLC : Rf 0.45 (chloroform : methanol = 9 : 1);  
 NMR(DMSO- $d_6$ ) :  $\delta$  7.79 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.11 (s, 1H), 6.90 (d, J = 3.3 Hz, 1H), 6.82 (s, 1H), 6.30-6.20 (m, 1H), 5.08 (s, 2H), 4.30-4.20 (m, 1H), 2.87 (t, J = 7.5 Hz, 2H), 2.79 (t, J = 7.5 Hz, 2H), 2.35 (s, 3H), 2.28 (s, 3H), 2.10-1.95 (m, 2H), 0.97 (d, J = 6.6 Hz, 6H).

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## Example 2(99)

3-methyl-4-[6-[N-isopropyl-N-(5-methyl-2-furysulfonyl)amino]indan-5-yloxymethyl] cinnamic acid

[0206]

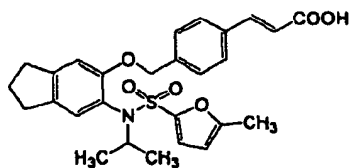


TLC : Rf 0.50 (chloroform : methanol = 9 : 1);  
NMR(DMSO- $d_6$ ) :  $\delta$  7.60-7.50 (m, 4H), 7.11 (s, 1H), 6.89 (d, J = 3.3 Hz, 1H), 6.80 (s, 1H), 6.52 (d, J = 16.2 Hz, 1H), 6.30-6.20 (m, 1H), 5.04 (d, J = 13.5 Hz, 1H), 5.01 (d, J = 13.5 Hz, 1H), 4.30-4.20 (m, 1H), 2.87 (t, J = 7.2 Hz, 2H), 2.78 (t, J = 7.2 Hz, 2H), 2.32 (s, 3H), 2.28 (s, 3H), 2.10-1.95 (m, 2H), 0.97 (d, J = 6.6 Hz, 6H).

## Example 2(100)

4-[6-[N-isopropyl-N-(5-methyl-2-furysulfonyl)amino]indan-5-yloxymethyl]cinnamic acid

[0207]

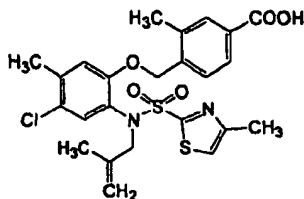


TLC Rf 0.42 (chloroform : methanol = 9 : 1);  
NMR :  $\delta$  7.79 (d, J = 16.2 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 6.89 (s, 1H), 6.84 (s, 1H), 6.80 (d, J = 3.3 Hz, 1H), 6.46 (d, J = 16.2 Hz, 1H), 6.02 (m, 1H), 5.14-5.00 (m, 2H), 4.46 (m, 1H), 2.91-2.80 (m, 4H), 2.31 (s, 3H), 2.14-2.02 (m, 2H), 1.11 (d, J = 6.6 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H).

## Example 2(101)

3-methyl-4-[2-[N-(2-methyl-2-propenyl)-N-(4-methyl-2-thiazolylsulfonyl)amino]-4-chloro-5-methylophenoxy] benzoic acid

[0208]

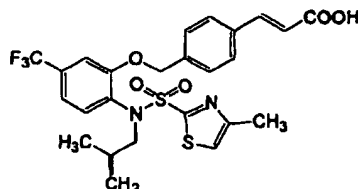


TLC : Rf 0.44 (chloroform: methanol = 9 : 1);  
NMR(DMSO- $d_6$ ) :  $\delta$  7.79 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.57 (s, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.27 (s, 1H), 7.23 (s, 1H), 4.97 (m, 2H), 4.77 (m, 1H), 4.72 (m, 1H), 4.21 (m, 2H), 2.34 (s, 3H), 2.32 (s, 3H), 2.22 (s, 3H), 1.68 (s, 3H).

## Example 2(102)

4-[2-[N-(2-methyl-2-propenyl)-N-(4-methyl-2-thiazolylsulfonyl)amino]-5-trifluoromethyl phenoxy]methyl]cinnamic acid

[0209]



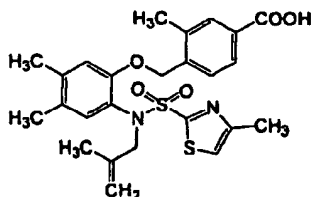
TLC : Rf 0.43 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.80 (d, J = 15.9 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.30-7.20 (m, 1H), 7.15 (s, 1H), 6.99 (s, 1H), 6.50 (d, J = 15.9 Hz, 1H), 4.97 (s, 2H), 4.77 (s, 1H), 4.72 (s, 1H), 4.37 (s, 2H), 2.35 (s, 3H), 1.77 (s, 3H).

## Example 2(103)

3-methyl-4-[2-[N-(2-methyl-2-propenyl)-N-(4-methyl-2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]benzoic acid

[0210]



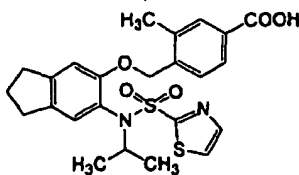
TLC : Rf 0.24 (dichloromethane : methanol = 19 : 1);

NMR(DMSO- $d_6$ ) :  $\delta$  7.77-7.73 (m, 2H), 7.50 (brs, 1H), 7.23 (d, J = 6.9 Hz, 1H), 6.99 (s, 1H), 6.96 (s, 1H), 4.87 (brs, 2H), 4.74 (brs, 1H), 4.71 (brs, 1H), 4.20 (brs, 2H), 2.28 (s, 3H), 2.19 (s, 3H), 2.16 (d, J = 0.6 Hz, 3H), 2.11 (s, 3H), 1.68 (s, 3H).

## Example 2(104)

3-methyl-4-[6-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]benzoic acid

[0211]



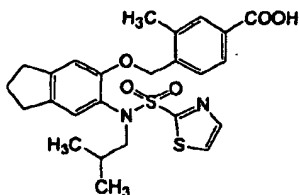
TLC : Rf 0.43 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.96 (d, J = 8.1 Hz, 1H), 7.93 (s, 1H), 7.89 (d, J = 3.0 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.46 (d, J = 3.0 Hz, 1H), 6.95 (s, 1H), 6.86 (s, 1H), 5.05 and 4.99 (each d, J = 13.5 Hz, each 1H), 4.69 (sept, J = 6.6 Hz, 1H), 2.94-2.79 (m, 4H), 2.39 (s, 3H), 2.16-2.02 (m, 2H), 1.18 and 1.15 (each d, J = 6.6 Hz, each 3H).

## Example 2(105)

3-methyl-4-[6-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]benzoic acid

[0212]



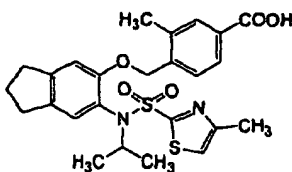
TLC: Rf 0.41 (chloroform: methanol = 9 : 1);

NMR:  $\delta$  7.93 (d, J = 8.4 Hz, 1H), 7.92 (s, 1H), 7.71 (d, J = 3.0 Hz, 1H), 7.35 (d, J = 3.0 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.15 (s, 1H), 6.77 (s, 1H), 5.02-4.64 (m, 2H), 3.81-3.43 (m, 2H), 2.95-2.76 (m, 4H), 2.34 (s, 3H), 2.17-2.01 (m, 2H), 1.82-1.64 (m, 1H), 1.08-0.83 (m, 6H).

## Example 2(106)

3-methyl-4-[6-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl] benzoic acid

[0213]



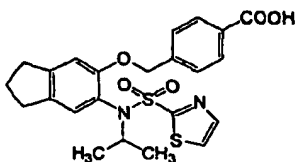
TLC : Rf 0.34 (dichloromethane : methanol = 19 : 1);

NMR:  $\delta$  7.97 (d, J = 8.1 Hz, 1H), 7.94 (s, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.00 (brs, 1H), 6.94 (s, 1H), 6.86 (s, 1H), 5.05 (d, J = 13.5 Hz, 1H), 4.99 (d, J = 13.5 Hz, 1H), 4.70 (m, 1H), 2.92-2.81 (m, 4H), 2.47 (s, 3H), 2.39 (s, 3H), 2.09 (m, 2H), 1.18 (d, J = 6.6 Hz, 3H), 1.15 (d, J = 6.6 Hz, 3H).

## Example 2(107)

4-[6-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]benzoic acid

[0214]



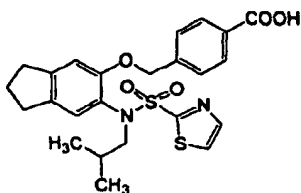
TLC: Rf 0.37 (chloroform: methanol = 10 : 1);

NMR:  $\delta$  8.13 (d, J = 8.1 Hz, 2H), 7.88 (d, J = 3.3 Hz, 1H), 7.51 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 3.3 Hz, 1H), 6.95 (s, 1H), 6.84 (s, 1H), 5.06 (d, J = 13.5 Hz, 1H), 5.05 (d, J = 13.5 Hz, 1H), 4.71 (m, 1H), 2.92-2.78 (m, 4H), 2.14-2.02 (m, 2H), 1.18 (d, J = 6.6 Hz, 3H), 1.16 (d, J = 6.6 Hz, 3H).

Example 2(108)

4-[6-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]benzoic acid

[0215]



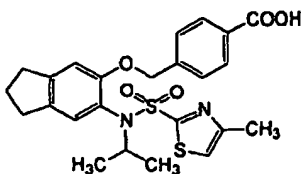
TLC: Rf 0.35 (chloroform : methanol = 10:1);

NMR:  $\delta$  8.11 (d, J = 8.1 Hz, 2H), 7.71 (d, J = 3.3 Hz, 1H), 7.35 (d, J = 3.3 Hz, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.15 (s, 1H), 6.75 (s, 1H), 4.97 (m, 1H), 4.77 (m, 1H), 3.80-3.47 (m, 2H), 2.89-2.82 (m, 4H), 2.15-2.01 (m, 2H), 1.73 (m, 1H), 1.05-0.85 (m, 6H).

Example 2(109)

4-[6-(N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino)indan-5-yloxymethyl]benzoic acid

[0216]



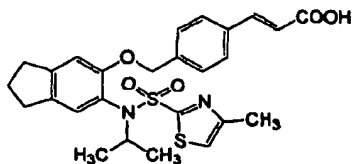
TLC : Rf 0.41 (chloroform: methanol =9:1);

NMR :  $\delta$  8.11 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 0.9 Hz, 1H), 6.94 (s, 1H), 6.84 (s, 1H), 5.11-5.00 (m, 2H), 4.71 (m, 1H), 2.91-2.79 (m, 4H), 2.47 (d, J = 0.9 Hz, 3H), 2.15-2.03 (m, 2H), 1.18 (d, J = 6.6 Hz, 3H), 1.15 (d, J = 6.6 Hz, 3H).

Example 2(110)

4-[6-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]cinnamic acid

[0217]



TLC : Rf 0.40 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.79 (d, J = 15.9 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 0.6 Hz, 1H), 6.92 (s, 1H), 6.85 (s, 1H), 6.47 (d, J = 15.9 Hz, 1H), 5.06-4.95 (m, 2H), 4.70 (m, 1H), 2.92-2.78 (m, 4H), 2.46 (d, J = 0.6 Hz, 3H), 2.16-2.01 (m, 2H), 1.17 (d, J = 6.6 Hz, 3H), 1.14 (d, J = 6.6 Hz, 3H).

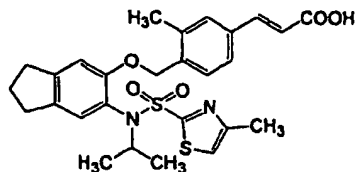


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## Example 2(111)

3-methyl-4-[6-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl] cinnamic acid

[0218]

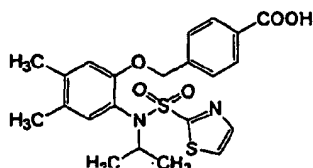


TLC : Rf 0.30 (dichloromethane : methanol = 19 : 1);  
NMR(DMSO-d<sub>6</sub>) : δ 12.38 (brs, 1H), 7.57 (brs, 1H), 7.56 (d, J = 15.9 Hz, 1H), 7.53 (s, 1H), 7.49 (brd, J = 8.1 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.13 (s, 1H), 6.83 (s, 1H), 6.53 (d, J = 15.9 Hz, 1H), 4.99 (brs, 2H), 4.47 (m, 1H), 2.87 (m, 2H), 2.77 (m, 2H), 2.37 (d, J = 0.9 Hz, 3H), 2.30 (s, 3H), 2.02 (m, 2H), 1.04 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H).

## Example 2(112)

4-[2-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]benzoic acid

[0219]

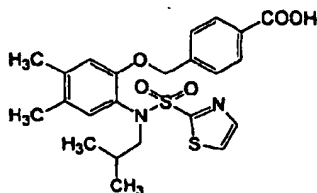


TLC : Rf 0.57 (chloroform : methanol = 9 : 1);  
NMR : δ 8.10 (d, J = 8.1 Hz, 2H), 7.86 (d, J = 3.0 Hz, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 3.0 Hz, 1H), 6.85 (s, 1H), 6.75 (s, 1H), 5.04 (s, 2H), 4.72 (sept, J = 6.9 Hz, 1H), 2.23 (s, 3H), 2.15 (s, 3H), 1.19 (d, J = 6.9 Hz, 3H), 1.15 (d, J = 6.9 Hz, 3H).

## Example 2(113)

4-[2-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]benzoic acid

[0220]



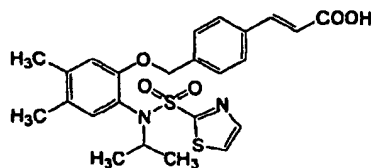
TLC : Rf 0.56 (chloroform : methanol = 9 : 1);  
NMR : δ 8.11 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 3.0 Hz, 1H), 7.36-7.32 (m, 3H), 7.07 (s, 1H), 6.66 (s, 1H), 5.10-4.65 (m, 2H), 3.80-3.45 (m, 2H), 2.22 (s, 3H), 2.18 (s, 3H), 1.71 (sept, J = 6.9 Hz, 1H), 1.15-0.95 (m, 6H).

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## Example 2(114)

4-[2-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]cinnamic acid

[0221]

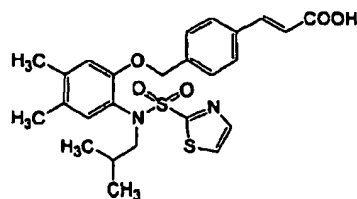


TLC : Rf 0.56 (chloroform : methanol = 9:1);  
NMR :  $\delta$  7.86 (d, J = 3.0 Hz, 1H), 7.79 (d, J = 15.9 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 3.0 Hz, 1H), 6.84 (s, 1H), 6.76 (s, 1H), 6.46 (d, J = 15.9 Hz, 1H), 5.04 (d, J = 11.7 Hz, 1H), 4.98 (d, J = 11.7 Hz, 1H), 4.71 (sept, J = 6.6 Hz, 1H), 2.23 (s, 3H), 2.13 (s, 3H), 1.18 (d, J = 6.6 Hz, 3H), 1.15 (d, J = 6.6 Hz, 3H).

## Example 2(115)

4-[2-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxy]methyl]cinnamic acid

[0222]

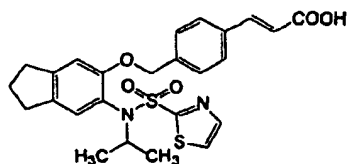


TLC : Rf 0.58 (chloroform: methanol = 9 : 1);  
NMR :  $\delta$  7.79 (d, J = 15.9 Hz, 1H), 7.67 (d, J = 3.0 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 3.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.05 (s, 1H), 6.67 (s, 1H), 6.47 (d, J = 15.9 Hz, 1H), 5.00-4.62 (m, 2H), 3.80-3.45 (m, 2H), 2.22 (s, 3H), 2.17 (s, 3H), 1.70 (sept, J = 6.6 Hz, 1H), 1.10-0.96 (m, 6H).

## Example 2(116)

4-[6-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]indan-5-yl]oxy]methyl]cinnamic acid

[0223]

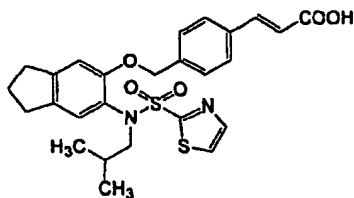


TLC : Rf 0.39 (chloroform : methanol = 10 : 1);  
NMR :  $\delta$  7.87 (d, J = 3.3 Hz, 1H), 7.80 (d, J = 15.9 Hz, 1H), 7.56 (d, J = 7.8 Hz, 2H), 7.45 (d, J = 7.8 Hz, 2H), 7.44 (d, J = 3.3 Hz, 1H), 6.94 (s, 1H), 6.85 (s, 1H), 6.48 (d, J = 15.9 Hz, 1H), 5.01 (d, J = 13.2 Hz, 1H), 5.00 (d, J = 13.2 Hz, 1H), 4.70 (m, 1H), 2.91-2.79 (m, 4H), 2.14-2.01 (m, 2H), 1.17 (d, J = 6.6 Hz, 3H), 1.15 (d, J = 6.6 Hz, 3H).

## Example 2(117)

4-[6-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]cinnamic acid

[0224]



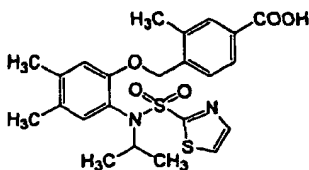
TLC : Rf 0.40 (chloroform : methanol = 10 : 1);

NMR :  $\delta$  7.80 (d, J = 15.9 Hz, 1H), 7.69 (d, J = 3.3 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 3.3 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.14 (s, 1H), 6.75 (s, 1H), 6.48 (d, J = 15.9 Hz, 1H), 4.92 (m, 1H), 4.70 (m, 1H), 3.78-3.46 (m, 2H), 2.90-2.80 (m, 4H), 2.14-2.01 (m, 2H), 1.72 (m, 1H), 1.02-0.83 (m, 6H).

## Example 2(118)

3-methyl-4-[2-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxy] benzoic acid

[0225]



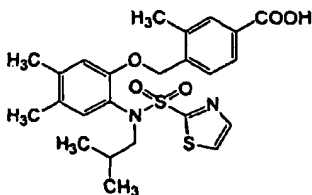
TLC: Rf 0.27 (chloroform: methanol = 9 : 1);

NMR :  $\delta$  8.00-7.90 (m, 2H), 7.87 (d, J = 3.0 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 3.0 Hz, 1H), 6.85 and 6.77 (each s, each 1H), 5.09-4.92 (m, 2H), 4.78-4.62 (m, 1H), 2.39 (s, 3H), 2.25 (s, 3H), 2.16 (s, 3H), 1.19 and 1.15 (each d, J = 6.6 Hz, each 3H).

## Example 2(119)

3-methyl-4-[2-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxy] benzoic acid

[0226]



TLC : Rf 0.27 (chloroform : methanol = 9 : 1);

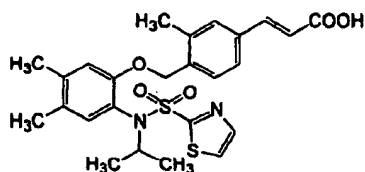
NMR :  $\delta$  7.95-7.89 (m, 2H), 7.70 and 7.34 (each d, J = 3.3 Hz, each 1H), 7.32-7.29 (m, 1H), 7.06 and 6.69 (each s, each 1H), 5.00-4.68 (m, 2H), 3.78-3.48 (m, 2H), 2.34 (s, 3H), 2.23 (s, 3H), 2.18 (s, 3H), 1.80-1.65 (m, 1H), 1.08-0.82 (m, 6H).

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## Example 2(120)

3-methyl-4-[2-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxy]methyl cinnamic acid

[0227]

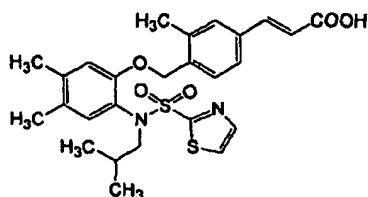


TLC : Rf 0.25 (chloroform : methanol = 9 : 1);  
NMR :  $\delta$  7.87 (d, J = 3.0 Hz, 1H), 7.77 (d, J = 16.2 Hz, 1H), 7.52-7.32 (m, 4H), 6.83 and 6.79 (each s, each 1H), 6.46 (d, J = 16.2 Hz, 1H), 5.05-4.87 (m, 2H), 4.75-4.62 (m, 1H), 2.36 (s, 3H), 2.25 (s, 3H), 2.15 (s, 3H), 1.17 and 1.13 (each d, J = 6.6 Hz, each 3H).

## Example 2(121)

3-methyl-4-[2-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxy]methyl cinnamic acid

[0228]

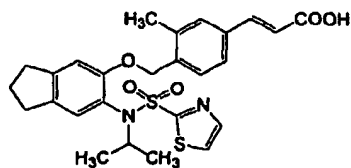


TLC : Rf 0.25 (chloroform : methanol = 9 : 1);  
NMR :  $\delta$  7.76 (d, J = 16.2 Hz, 1H), 7.69 (d, J = 3.0 Hz, 1H), 7.42-7.35 (m, 2H), 7.34 (d, J = 3.0 Hz, 1H), 7.25-7.19 (m, 1H), 7.05 and 6.70 (each s, each 1H), 6.47 (d, J = 16.2 Hz, 1H), 4.95-4.62 (m, 2H), 3.75-3.48 (m, 2H), 2.31 (s, 3H), 2.24 (s, 3H), 2.18 (s, 3H), 1.78-1.62 (m, 1H), 1.78-1.62 (m, 6H).

## Example 2(122)

3-methyl-4-[6-[N-isopropyl-N-(2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl cinnamic acid

[0229]



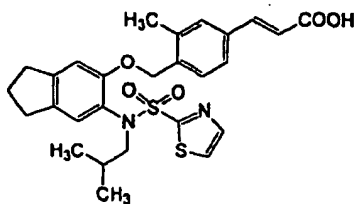
TLC: Rf 0.44 (chloroform methanol = 9 : 1);  
NMR :  $\delta$  7.88 (d, J = 3.0 Hz, 1H), 7.77 (d, J = 16.2 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 3.0 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.38 (s, 1H), 6.93 (s, 1H), 6.87 (s, 1H), 6.46 (d, J = 16.2 Hz, 1H), 5.02 and 4.95 (each d, J = 12.9 Hz, each 1H), 4.68 (sept, J = 6.6 Hz, 1H), 2.94-2.78 (m, 4H), 2.36 (s, 3H), 2.16-2.02 (m, 2H), 1.17 and 1.14 (each d, J = 6.6 Hz, each 3H).

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## Example 2(123)

3-methyl-4-[6-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]cinnamic acid

[0230]



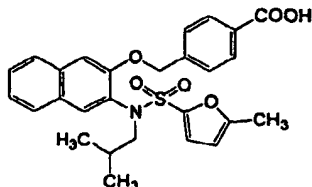
TLC : Rf 0.39 (chloroform : methanol = 9 : 1);

NMR(DMSO- $d_6$ ) :  $\delta$  7.98 (d, J = 3.0 Hz, 1H), 7.87 (d, J = 3.0 Hz, 1H), 7.56 (d, J = 16.2 Hz, 1H), 7.52 (s, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 8.1 Hz, 1H), 7.06 (s, 1H), 7.00 (s, 1H), 6.54 (d, J = 16.2 Hz, 1H), 5.04-4.66 (m, 2H), 3.57-3.37 (m, 2H), 2.93-2.68 (m, 4H), 2.27 (s, 3H), 2.11-1.93 (m, 2H), 1.64-1.46 (m, 1H), 0.94-0.74 (m, 6H).

## Example 2(124)

4-[3-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-2-naphthyloxymethyl]benzoic acid

[0231]



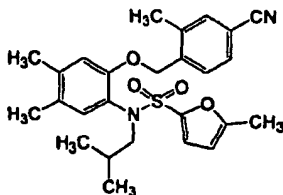
TLC : Rf 0.33 (chloroform: methanol = 9 : 1);

NMR(CD<sub>3</sub>OD) :  $\delta$  8.05 (d, J = 8.4 Hz, 2H), 7.82-7.75 (m, 3H), 7.53 (d, J = 8.4 Hz, 2H), 7.51-7.35 (m, 3H), 6.71 (d, J = 3.3 Hz, 1H), 6.05 (m, 1H), 5.42-4.95 (br, 2H), 3.62 (d, J = 7.5 Hz, 2H), 2.13 (s, 3H), 1.79-1.61 (m, 1H), 0.94 (d, J = 6.3 Hz, 6H).

## Reference example 4

N-[4,5-dimethyl-2-(2-methyl-4-cyanophenylmethoxy)phenyl]-N-isobutyl-(5-methyl-2-furyl) sulfonylamide

[0232]



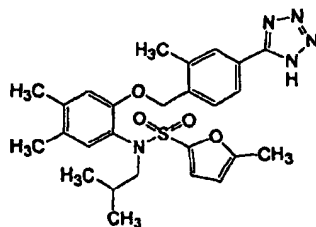
[0233] Under atmosphere of argon, a solution of 3-methyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-

4,5-dimethylphenoxy)methyl]benzoic acid prepared in example 2 (178 mg) in dichloromethane (1.5 ml) was cooled to 0°C, then oxalyl chloride (48  $\mu$ l) and a catalytic amount of N,N-dimethylformamide was added thereto. After the solution was stirred for 1 hour at room temperature, the reaction mixture was concentrated under reduced pressure, and azeotroped with toluene. Under atmosphere of argon, the residue was dissolved in dichloromethane (1.5 ml), and cooled to 0°C. The solution was added by 28% aqueous ammonia (1ml) and stirred for 5 minutes. The solution was added by water and ethyl acetate. The organic layer was washed, dried and concentrated under reduced pressure. Under atmosphere of argon, the residue was dissolved in dichloromethane (1.5 ml), and cooled to 0°C. The solution was added by pyridine (0.18 ml) and trifluoromethanesulfonic acid anhydride (0.12 ml) and stirred for 50 minutes. The reaction mixture was poured into water, then it was added by ethyl acetate. The organic layer was washed, dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane - ethyl acetate) to give the title compound (149 mg) having the following physical data. TLC: Rf 0.74 (n-hexane: ethyl acetate = 1 : 1).

### Example 3

N-[4,5-dimethyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide

[0234]



[0235] To N-[4,5-dimethyl-2-(2-methyl-4-cyanophenylmethoxy)phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide prepared in reference example 4 (79 mg), trimethyltin azide (43 mg) was added, and mixture was refluxed for 7 hours, then stirred for 1 day at room temperature. The reaction mixture was added by methanol (3 ml) and 2N hydrochloric acid (2 ml), then stirred for 2 hours. The solution was added by water and ethyl acetate. The organic layer was washed, dried and concentrated under reduced pressure. The residue was washed by hexane - ethyl acetate to give the title compound (81 mg) having the following physical data. TLC: Rf 0.52 (chloroform: methanol: water = 8 : 2 : 0.2); MS (FAB, Pos.): 510 (M + H)<sup>+</sup>.

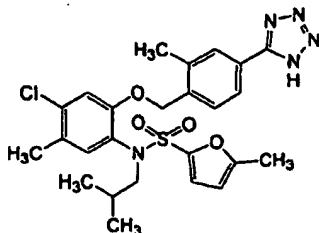
Example 3(1) ~ Example 3(38)

[0236] By the same procedures as described in reference examples 1 - 3 and example 3, the title compounds having the following physical data were obtained.

Example 3(1)

N-[4-chloro-5-methyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide

[0237]



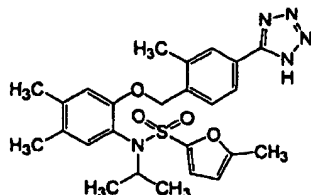
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TLC: Rf 0.40 (dichloromethane : methanol = 10 : 1);  
MS (FAB, Pos.): 530 (M)<sup>+</sup>.

## Example 3(2)

N-[4,5-dimethyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-(5-methyl-2-furyl)sulfonylamide

[0238]

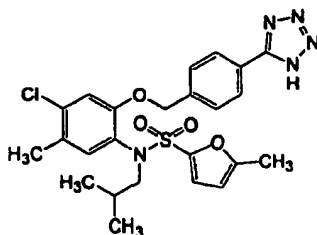


TLC : Rf 0.52 (chloroform : methanol : water = 8 : 2 : 0.2);  
MS (FAB, Pos.) : 496 (M + H)<sup>+</sup>.

## Example 3(3)

N-[4-chloro-5-methyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide

[0239]

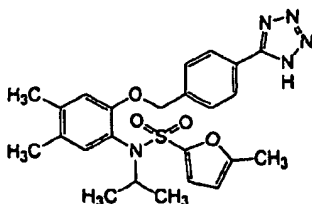


TLC : Rf 0.39 (chloroform : methanol : water = 8 : 2 : 0.2);  
NMR :  $\delta$  8.05 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.08 (s, 1H), 6.93 (s, 1H), 6.80 (d, J = 3.3 Hz, 1H), 6.01 (m, 1H), 5.15-4.80 (br, 2H), 3.46 (d, J = 7.2 Hz, 2H), 2.27 (s, 3H), 2.19 (s, 3H), 1.64 (m, 1H), 0.88 (d, J = 6.9 Hz, 6H).

## Example 3(4)

N-[4,5-dimethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-(5-methyl-2-furyl)sulfonylamide

[0240]



TLC : Rf 0.41 (chloroform : methanol : water = 8 : 2 : 0.2);  
NMR(DMSO-d<sub>6</sub>) :  $\delta$  8.04 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.1 Hz, 2H), 7.01 (s, 1H), 6.91 (d, J = 3.3 Hz, 1H), 6.76 (s, 1H), 6.29-6.23 (m, 1H), 5.18 and 5.12 (each d, J = 13.5 Hz, each 1H), 4.30 (sept, J = 6.6 Hz, 1H), 2.30 (s, 3H), 2.23

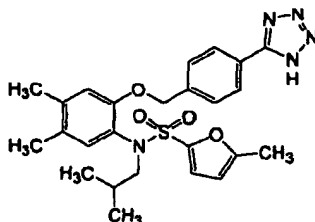
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(s, 3H), 2.14 (s, 3H), 1.02 and 1.00 (each d, J = 6.6 Hz, each 3H).

## Example 3(5)

5 N-[4,5-dimethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide

[0241]



TLC : Rf 0.37 (chloroform : methanol : water = 8 : 2 : 0.2);

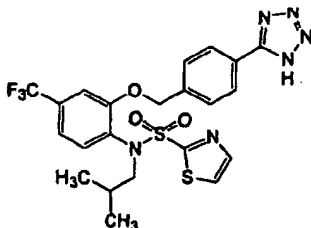
20 NMR(DMSO-d<sub>6</sub>) : δ 8.04 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 6.96 (s, 1H), 6.92 (s, 1H), 6.82 (d, J = 3.3 Hz, 1H), 6.19-6.13 (m, 1H), 5.28-4.82 (m, 2H), 3.38 (d, J = 6.9 Hz, 2H), 2.21 (s, 3H), 2.14 (s, 6H), 1.64-1.44 (m, 1H), 0.85 (d, J = 6.6 Hz, 6H).

## Example 3(6)

25

N-[4-trifluoromethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-2-thiazolylsulfonylamide

[0242]



40

TLC: Rf 0.46 (chloroform : methanol : water = 8 : 2 : 0.2);

NMR : δ 8.09 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 2.7 Hz, 1H), 7.49-7.44 (m, 4H), 7.27 (m, 1H), 7.19 (s, 1H), 5.01 (br, 2H), 3.63 (d, J = 7.2 Hz, 2H), 1.67 (m, 1H), 0.97 (d, J = 7.2 Hz, 6H).

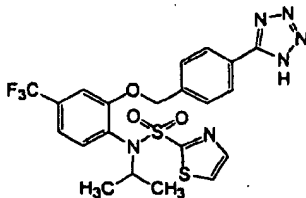
## Example 3(7)

45

N-[4-trifluoromethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-2-thiazolylsulfonylamide

[0243]

50



55



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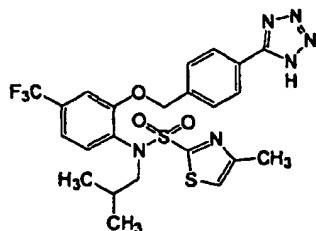
TLC : Rf 0.31 (chloroform : methanol : water = 8 : 2 : 0.2);

NMR :  $\delta$  8.07 (d, J = 8.1 Hz, 2H), 7.94 (d, J = 3.3 Hz, 1H), 7.60 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 3.3 Hz, 1H), 7.36-7.20 (m, 3H), 5.17 and 5.13 (each d, J = 12.0 Hz, each 1H), 4.68 (sept, J = 6.6 Hz, 1H), 1.15 and 1.14 (each d, J = 6.6 Hz, each 3H).

Example 3(8)

N-[4-trifluoromethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide

[0244]



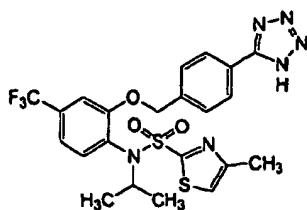
TLC : Rf 0.31 (chloroform : methanol : water = 8 : 2 : 0.2);

NMR :  $\delta$  8.04 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 8.1 Hz, 2H), 7.23 (m, 1H), 7.16 (s, 1H), 6.99 (s, 1H), 4.95 (br, 2H), 3.56 (d, J = 6.6 Hz, 2H), 2.26 (s, 3H), 1.59 (sept, J = 6.6 Hz, 1H), 0.84 (d, J = 6.6 Hz, 6H).

Example 3(9)

N-[4-trifluoromethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide

[0245]



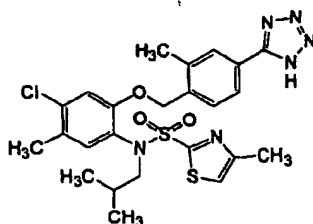
TLC: Rf 0.42 (chloroform: methanol: water = 8 : 2 : 0.2);

NMR :  $\delta$  7.93 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.24-7.16 (m, 3H), 7.02 (s, 1H), 5.10-4.92 (m, 2H), 4.57 (quint, J = 6.6 Hz, 1H), 2.39 (s, 3H), 1.04 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H).

Example 3(10)

N-[4-chloro-5-methyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide

[0246]

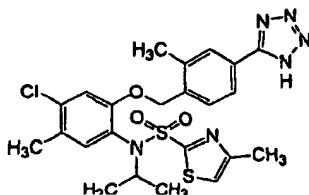


TLC : Rf 0.24 (dichloromethane : methanol = 10 : 1);  
MS (FAB, Pos.) : 547 (M)<sup>+</sup>.

Example 3(11)

N-[4-chloro-5-methyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide

[0247]

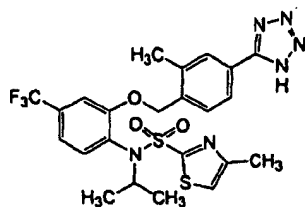


TLC : Rf 0.24 (dichloromethane : methanol = 10 : 1);  
MS (FAB, Pos.): 533 (M)<sup>+</sup>.

Example 3(12)

N-[4-trifluoromethyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide

[0248]



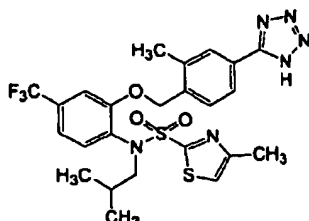
TLC: Rf 0.38 (chloroform: methanol: water = 8:2: 0.2);

NMR :  $\delta$  7.91 (s, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.33-7.20 (m, 3H), 7.12 (s, 1H), 5.11 (s, 2H), 4.65 (sept, J = 6.6 Hz, 1H), 2.49 (s, 3H), 2.43 (s, 3H), 1.12 (d, J = 6.6 Hz, 6H).

Example 3(13)

N-[4-trifluoromethyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide

[0249]



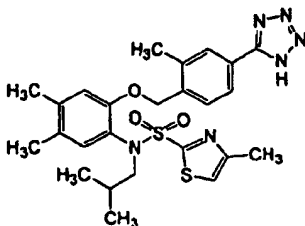
TLC : Rf 0.34 (chloroform : methanol : water = 8 : 2 : 0.2);

NMR :  $\delta$  7.97 (s, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.48-7.38 (m, 2H), 7.34-7.18 (m, 2H), 7.05 (s, 1H), 5.12-4.84 (m, 2H), 3.59 (d, J = 7.2 Hz, 2H), 2.41 (s, 3H), 2.34 (s, 3H), 1.74-1.58 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H).

Example 3(14)

N-[4,5-dimethyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide

[0250]



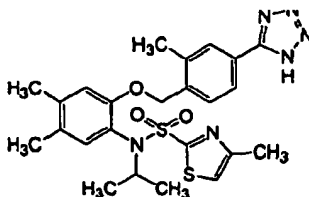
TLC : Rf 0.46 (chloroform : methanol : water = 8 : 2 : 0.2);

MS (FAB, Pos.) : 527 (M + H)<sup>+</sup>.

Example 3(15)

N-[4,5-dimethyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide

[0251]



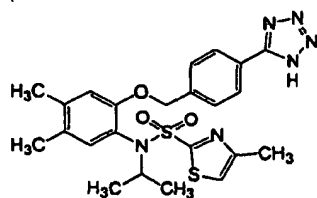
TLC : Rf 0.52 (chloroform : methanol : water = 8 : 2 : 0.2);

MS (FAB, Pos.) : 513 (M + H)<sup>+</sup>.

Example 3(16)

N-[4,5-dimethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide

[0252]

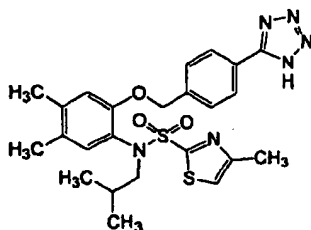


TLC : Rf 0.29 (chloroform : methanol = 5 : 1);  
MS(APCI, Neg. 20V) : 497 (M - H)<sup>-</sup>.

Example 3(17)

N-[4,5-dimethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide

[0253]

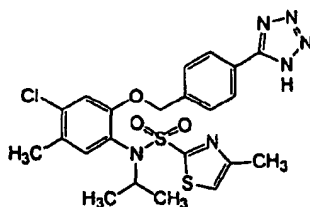


TLC: Rf 0.26 (chloroform: methanol = 5 : 1);  
MS(APCI, Neg. 20V) : 511 (M - H)<sup>-</sup>.

Example 3(18)

N-[4-chloro-5-methyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide

[0254]



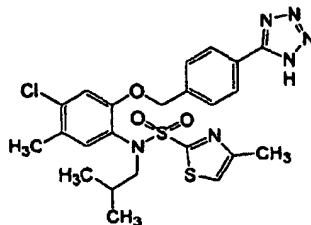
TLC : Rf 0.31 (chloroform : methanol water = 8 : 2 : 0.2);  
NMR :  $\delta$  8.02 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.10 (s, 1H), 6.98 (s, 2H), 5.03 and 4.95 (each d, J = 12.6 Hz, each 1H), 4.65 (sept, J = 6.6 Hz, 1H), 2.46 (s, 3H), 2.26 (s, 3H), 1.13 and 1.12 (each d, J = 6.6 Hz, each 3H).

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## Example 3(19)

N-[4-chloro-5-methyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]methoxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide

[0255]



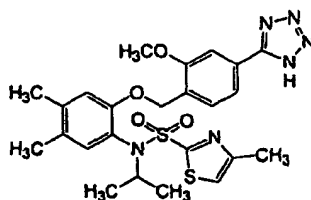
TLC : Rf 0.29 (chloroform : methanol : water = 8 : 2 : 0.2);

NMR(DMSO- $d_6$ ) :  $\delta$  8.05 (d, J = 8.4 Hz, 2H), 7.52 (s, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.26 (s, 1H), 7.25 (s, 1H), 5.25-4.73 (m, 2H), 3.62-3.40 (m, 2H), 2.26 (s, 3H), 2.22 (s, 3H), 1.66-1.50 (m, 1H), 0.88 (d, J = 6.6 Hz, 6H).

## Example 3(20)

N-[4,5-dimethyl-2-[2-methoxy-4-(5-tetrazolyl)phenylmethoxy]phenyl]methoxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide

[0256]



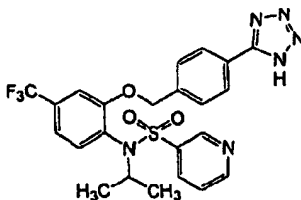
TLC : Rf 0.31 (chloroform : methanol = 5 : 1);

NMR(CDCl<sub>3</sub> + 1 drop of CD<sub>3</sub>OD) :  $\delta$  7.71 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 1.5 Hz, 1H), 7.51 (dd, J = 7.5, 1.5 Hz, 1H), 7.07 (d, J = 0.9 Hz, 1H), 6.83 (s, 1H), 6.82 (s, 1H), 5.09 (d, J = 13.8 Hz, 1H), 5.04 (d, J = 13.8 Hz, 1H), 4.68 (m, 1H), 3.97 (s, 3H), 2.46 (d, J = 0.9 Hz, 3H), 2.25 (s, 3H), 2.16 (s, 3H), 1.15 (d, J = 6.6 Hz, 3H), 1.14 (d, J = 6.6 Hz, 3H).

## Example 3(21)

N-[4-trifluoromethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]methoxy]phenyl]-N-isopropyl-3-pyridylsulfonylamide

[0257]



TLC : Rf 0.47 (chloroform : methanol = 3 : 1);

NMR(DMSO- $d_6$ ) :  $\delta$  8.91 (dd, J = 2.4, 0.6 Hz, 1H), 8.73 (dd, J = 4.5, 1.8 Hz, 1H), 8.14 (ddd, J = 8.4, 2.4, 1.8 Hz, 1H),

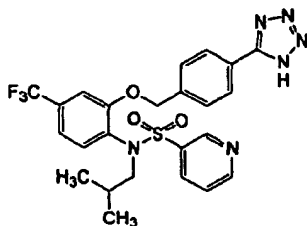
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8.04 (d, J = 8.4 Hz, 2H), 7.57 (s, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.47 (ddd, J = 8.4, 4.5, 0.6 Hz, 1H), 7.43-7.38 (m, 2H), 5.28 (d, J = 12.3 Hz, 1H), 5.21 (d, J = 12.3 Hz, 1H), 4.45-4.25 (m, 1H), 1.04 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H).

## Example 3(22)

N-[4-trifluoromethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-3-pyridylsulfonamide

[0258]



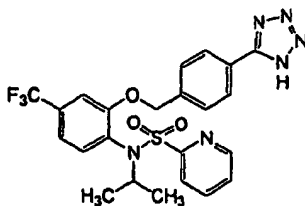
TLC : Rf 0.47 (chloroform : methanol = 3 : 1);

NMR:  $\delta$  8.89 (d, J = 1.5 Hz, 1H), 8.46 (dd, J = 4.8, 1.5 Hz, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.83 (dt, J = 8.1, 1.5 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.35 (dd, J = 8.4, 0.9 Hz, 1H), 7.26-7.20 (m, 1H), 7.19 (d, J = 0.9 Hz, 1H), 7.14 (d, J = 8.4 Hz, 2H), 4.95 (brs, 1H), 4.77 (brs, 1H), 3.56 (brs, 1H), 3.40 (brs, 1H), 1.70-1.60 (m, 1H), 0.94 (brs, 6H).

## Example 3(23)

N-[4-trifluoromethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-2-pyridylsulfonamide

[0259]



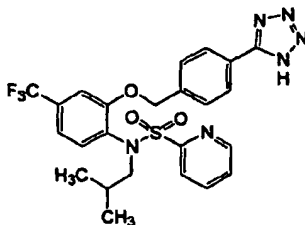
TLC : Rf 0.47 (chloroform : methanol = 3 : 1);

NMR:  $\delta$  8.69 (d, J = 4.8 Hz, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.92-7.76 (m, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.46-7.38 (m, 1H), 7.30-7.26 (m, 3H), 5.08 (d, J = 12.0 Hz, 1H), 5.01 (d, J = 12.0 Hz, 1H), 4.75-4.55 (m, 1H), 1.11 (d, J = 7.5 Hz, 3H), 1.08 (d, J = 7.5 Hz, 3H).

Example 3(24)

N-[4-trifluoromethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-2-pyridylsulfonylamide

[0260]



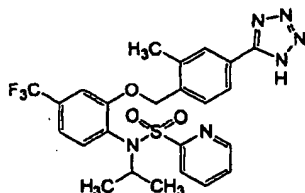
TLC : Rf 0.38 (chloroform : methanol = 3 : 1);

NMR :  $\delta$  8.60-8.45 (m, 1H), 8.10 (d, J = 8.4 Hz, 2H), 7.80-7.70 (m, 2H), 7.49 (d, J = 8.1 Hz, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.38-7.31 (m, 1H), 7.30-7.20 (m, 1H), 7.14 (d, J = 1.8 Hz, 1H), 4.91 (brs, 2H), 3.63 (brd, J = 6.3 Hz, 2H), 1.70-1.55 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H).

Example 3(25)

N-[4-trifluoromethyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-2-pyridylsulfonylamide

[0261]



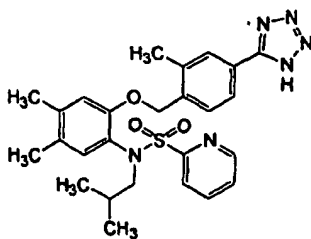
TLC: Rf 0.24 (chloroform: methanol = 3 : 1);

NMR:  $\delta$  8.69 (d, J = 4.8 Hz, 1H), 7.92-7.75 (m, 4H), 7.58 (d, J = 7.8 Hz, 1H), 7.48-7.39 (m, 1H), 7.31-7.18 (m, 3H), 5.03 (s, 2H), 4.72-4.58 (m, 1H), 2.37 (s, 3H), 1.11 and 1.09 (each d, J = 6.6 Hz, each 3H).

Example 3(26)

N-[4,5-dimethyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-2-pyridylsulfonylamide

[0262]



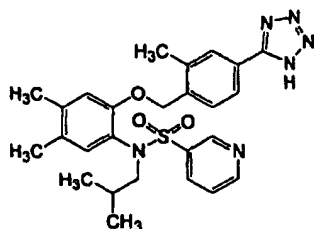
TLC : Rf 0.40 (chloroform : methanol : water = 8 : 2 : 0.2);

MS (FAB, Pos.) : 507 (M + H)<sup>+</sup>.

Example 3(27)

N-[4,5-dimethyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-3-pyridylsulfonylamine

[0263]



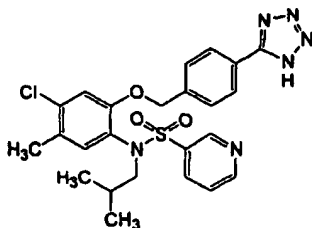
TLC : Rf 0.44 chloroform : methanol: water = 8 : 2 : 0.2);

MS (FAB, Pos.) : 507 (M + H)<sup>+</sup>.

Example 3(28)

N-[4-chloro-5-methyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-3-pyridylsulfonylamine

[0264]



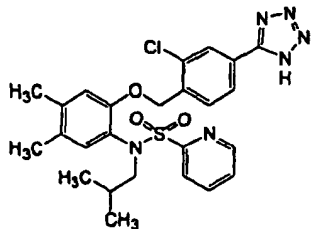
TLC : Rf 0.28 (chloroform : methanol: water = 8 : 2 : 0.2);

NMR(DMSO-d<sub>6</sub>) : δ 8.69 (d, J = 1.8 Hz, 1H), 8.64 (dd, J = 4.8, 1.8 Hz, 1H), 8.00 (d, J = 8.1 Hz, 2H), 7.98-7.92 (m, 1H), 7.40 (dd, J = 8.1, 4.8 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.27 (s, 1H), 7.24 (s, 1H), 5.17-4.68 (m, 2H), 3.46-3.16 (m, 2H), 2.28 (s, 3H), 1.60-1.42 (m, 1H), 1.00-0.73 (m, 6H).

Example 3(29)

N-[4,5-dimethyl-2-[2-chloro-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-2-pyridylsulfonylamine

[0265]





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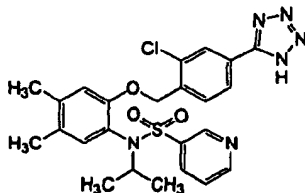
TLC : Rf 0.22 (chloroform : methanol : water = 40 : 10 : 1);

NMR :  $\delta$  8.52 (d, J = 4.5 Hz, 1H), 8.20 (d, J = 1.5 Hz, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.79 (dt, J = 1.5, 8.1 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.35-7.30 (m, 1H), 7.04 (s, 1H), 6.63 (s, 1H), 4.90 (br, 1H), 4.64 (br, 1H), 3.67 (br, 1H), 3.57 (br, 1H), 2.21 (s, 3H), 2.15 (s, 3H), 1.80-1.60 (m, 1H), 0.91 (br, 6H).

Example 3(30)

N-[4,5-dimethyl-2-[2-chloro-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-3-pyridylsulfonylamide

[0266]



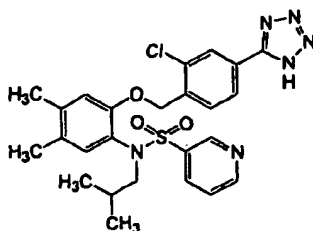
TLC: Rf 0.22 (chloroform: methanol: water = 40 : 10 : 1);

NMR:  $\delta$  9.11 (d, J = 1.8 Hz, 1H), 8.61 (dd, J = 4.8, 1.5 Hz, 1H), 8.20-8.10 (m, 2H), 7.88 (dd, J = 7.8, 1.5 Hz, 1H), 7.42 (dd, J = 8.1, 4.8 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.01 (s, 1H), 6.79 (s, 1H), 4.96 (d, J = 13.5 Hz, 1H), 4.93 (d, J = 13.5 Hz, 1H), 4.60-4.45 (m, 1H), 2.29 (s, 3H), 2.23 (s, 3H), 1.25 (d, J = 6.6 Hz, 3H), 1.11 (d, J = 6.6 Hz, 3H).

Example 3(31)

N-[4,5-dimethyl-2-[2-chloro-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-3-pyridylsulfonylamide

[0267]



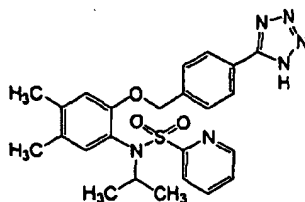
TLC : Rf 0.22 (chloroform : methanol: water = 40 : 10 : 1);

NMR :  $\delta$  8.97 (d, J = 1.8 Hz, 1H), 8.55-8.45 (m, 1H), 8.15 (d, J = 1.5 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.83 (dt, J = 8.1, 1.8 Hz, 1H), 7.31 (dd, J = 8.1, 4.8 Hz, 1H), 7.24 (s, 1H), 7.07 (d, J = 7.8 Hz, 1H), 6.75 (s, 1H), 4.89 (d, J = 12.5 Hz, 1H), 4.63 (d, J = 12.5 Hz, 1H), 3.70-3.60 (m, 1H), 3.45-3.30 (m, 1H), 2.30 (s, 3H), 2.26 (s, 3H), 1.80-1.60 (m, 1H), J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H).

Example 3(32)

N-[4,5-dimethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-2-pyridylsulfonamide

[0268]

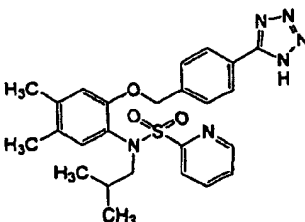


TLC : Rf 0.23 (chloroform : methanol = 5 : 1);  
MS(APCI, Neg. 20V) : 477 (M - H)<sup>-</sup>.

Example 3(33)

N-[4,5-dimethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-2-pyridylsulfonamide

[0269]

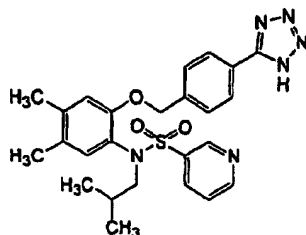


TLC: Rf 0.23 (chloroform: methanol = 5 : 1);  
MS(APCI, Neg. 20V): 491 (M - H)<sup>-</sup>.

Example 3(34)

N-[4,5-dimethyl-2-[4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-3-pyridylsulfonamide

[0270]



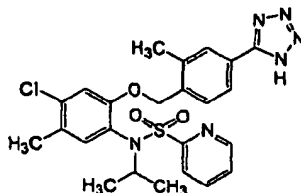
TLC: Rf 0.23 (chloroform: methanol = 5 : 1);  
MS(APCI, Neg. 20V) : 491 (M - H)<sup>-</sup>.

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## Example 3(35)

N-[4-chloro-5-methyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-2-pyridylsulfonylamide

[0271]



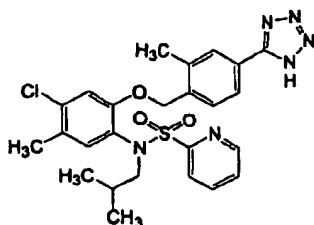
TLC: Rf 0.30 (chloroform: methanol: water = 8 : 2 : 0.2);

NMR(DMSO- $d_6$ ):  $\delta$  8.67 (d, J = 3.6 Hz, 1H), 7.98-7.88 (m, 2H), 7.85-7.78 (m, 2H), 7.55-7.48 (m, 2H), 7.37 (s, 1H), 7.04 (s, 1H), 5.10 (ABd, J = 13.2 Hz) and 5.04 (ABd, J = 13.2 Hz) total 2H, 4.49 (sept, J = 6.9 Hz, 1H), 2.36 (s, 3H), 2.23 (s, 3H), 1.02 (d, J = 6.9 Hz) and 0.99 (d, J = 6.9 Hz) total 6H.

## Example 3(36)

N-[4-chloro-5-methyl-2-[2-methyl-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-2-pyridylsulfonylamide

[0272]



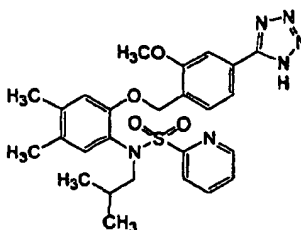
TLC : Rf 0.26 (chloroform : methanol: water = 8 : 2 : 0.2);

NMR(DMSO- $d_6$ ):  $\delta$  8.48 (m, 1H), 7.93-7.85 (m) and 7.90 (dd, J = 7.8, 1.8 Hz) total 2H, 7.81 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.44 (ddd, J = 7.8, 4.8, 1.2 Hz, 1H), 7.29 (s) and 7.27 (d, J = 7.8 Hz) total 2H, 7.20 (s, 1H), 4.92 (m, 2H), 3.47 (m, 2H), 2.31 (s, 3H), 2.23 (s, 3H), 1.50 (m, 1H), 0.81 (d, J = 6.6 Hz, 6H).

## Example 3(37)

N-[4,5-dimethyl-2-[2-methoxy-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isobutyl-2-pyridylsulfonylamide

[0273]



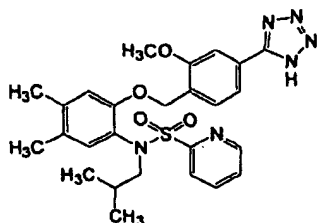
TLC : Rf 0.23 (dichloromethane : methanol = 10 : 1);

MS (FAB, Pos.) : 523 (M + H)<sup>+</sup>.

Example 3(38)

N-[4,5-dimethyl-2-[2-methoxy-4-(5-tetrazolyl)phenylmethoxy]phenyl]-N-isopropyl-2-pyridylsulfonylamide

[0274]

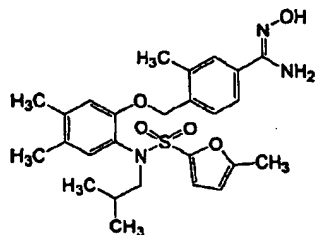


TLC: Rf 0.23 (chloroform: methanol = 10 : 1).

Reference example 5

N-[4,5-dimethyl-2-[2-methyl-4-(N-hydroxyamidino)phenylmethoxy]phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide

[0275]



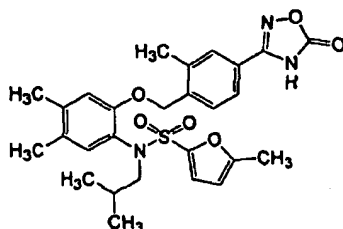
[0276] To a solution of N-[4,5-dimethyl-2-(2-methyl-4-cyanophenylmethoxy)phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide prepared in reference example 4 (70 mg) in ethanol (2 ml), triethylamine (42  $\mu$ l) and hydroxylamine hydrogen chloride salt (21 mg) were added at room temperature, then mixture was refluxed for 5 hours. After termination of reaction, the reaction mixture was poured into ethyl acetate - water. The organic layer was washed, dried and concentrated under reduced pressure to give the title compound (80 mg) having the following physical data.

TLC : Rf 0.38 (n-hexane : ethyl acetate = 2 : 3).

## Example 4

N-[4,5-dimethyl-2-[2-methyl-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide

[0277]



[0278] To a solution of N-[4,5-dimethyl-2-[2-methyl-4-(N-hydroxyamidino)phenylmethoxy]phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide prepared in reference example 5 (78 mg) in N,N-dimethylformamide (1 ml), pyridine (16  $\mu$ l) and chloro formic acid 2-ethylhexyl ester (30  $\mu$ l) were added and the mixture was stirred for 1 hour at 0°C. After termination of reaction, the reaction mixture was poured into ethyl acetate - water. The organic layer was washed, dried and concentrated under reduced pressure. To the residue, xylene (2 ml) was added, and the mixture was refluxed for 6 hours at 140°C. After termination of reaction, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane - ethyl acetate) to give the title compound (42 mg) having the following physical data.

TLC : Rf 0.43 (chloroform : methanol = 19 : 1);

NMR :  $\delta$  10.69 (br, 1H), 7.62 (s, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 6.97 (s, 1H), 6.78 (d, J = 3.3 Hz, 1H), 6.71 (s, 1H), 6.00 (d, J = 3.3 Hz, 1H), 4.94 (br, 2H), 3.46 (d, J = 7.5 Hz, 2H), 2.39 (s, 3H), 2.24 (s, 3H), 2.19 (s, 3H), 2.18 (s, 3H), 1.70-1.55 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H).

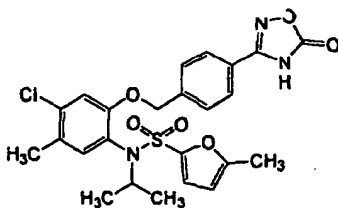
Example 4(1) ~ Example 4(22)

[0279] By the same procedures as described in reference examples 1 - 5 and example 4, the compounds having the following physical data were obtained.

Example 4(1)

N-[4-chloro-5-methyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isopropyl-(5-methyl-2-furyl)sulfonylamide

[0280]



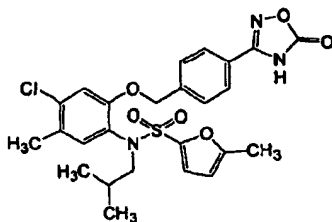
TLC : Rf 0.40 (chloroform : methanol = 19 : 1);

NMR :  $\delta$  10.81 (br, 1H), 7.79 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.3 Hz, 2H), 6.97 (s, 1H), 6.92 (s, 1H), 6.84 (d, J = 3.3 Hz, 1H), 6.10-6.00 (m, 1H), 5.07 (s, 2H), 4.55-4.35 (m, 1H), 2.34 (s, 3H), 2.28 (s, 3H), 1.10 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.6 Hz, 3H).

## Example 4(2)

N-[4-chloro-5-methyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide

[0281]



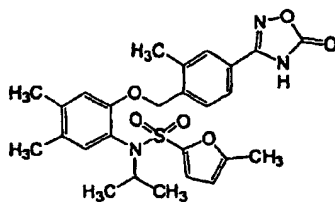
TLC : Rf 0.38 (chloroform : methanol = 19 : 1);

NMR :  $\delta$  11.01 (br, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.3 Hz, 2H), 7.10 (s, 1H), 6.92 (s, 1H), 6.78 (d, J = 3.3 Hz, 1H), 6.05-5.95 (m, 1H), 5.02 (br, 2H), 3.45 (d, J = 7.2 Hz, 2H), 2.29 (s, 3H), 2.20 (s, 3H), 1.70-1.55 (m, 1H), 0.90 (d, J = 6.9 Hz, 6H).

## Example 4(3)

N-[4,5-dimethyl-2-[2-methyl-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isopropyl-(5-methyl-2-furyl)sulfonylamide

[0282]



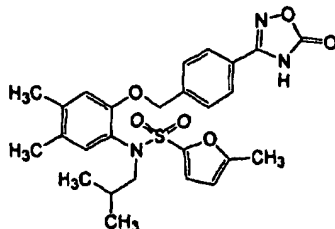
TLC : Rf 0.43 (chloroform : methanol = 19 : 1);

NMR :  $\delta$  10.34 (br, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.65-7.55 (m, 2H), 6.86 (d, J = 3.3 Hz, 1H), 6.79 (s, 1H), 6.74 (s, 1H), 6.10-6.05 (m, 1H), 4.93 (s, 2H), 4.50-4.40 (m, 1H), 2.37 (s, 3H), 2.34 (s, 3H), 2.26 (s, 3H), 2.17 (s, 3H), 1.09 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.6 Hz, 3H).

## Example 4(4)

N-[4,5-dimethyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide

[0283]



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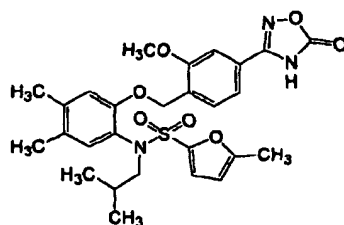
TLC Rf 0.53 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  11.10-10.50 (br, 1H, NH), 7.78 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 8.7 Hz, 2H), 6.97 (s, 1H), 6.78 (d, J = 3.3 Hz, 1H), 6.69 (s, 1H), 6.01-5.98 (m, 1H), 5.15-4.85 (m, 2H), 3.46 (d, J = 7.2 Hz, 2H), 2.22 (s, 3H), 2.20 (s, 3H), 2.17 (s, 3H), 1.73-1.60 (m, 1H), 0.90 (d, J = 6.9 Hz, 6H).

Example 4(5)

N-[4,5-dimethyl-2-[2-methoxy-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isobutyl-(5-methyl-2-furyl)sulfonylamide

[0284]



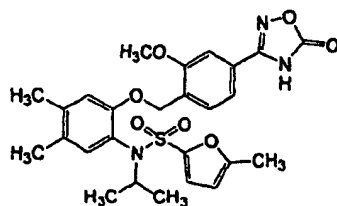
TLC : Rf 0.46 (dichloromethane : methanol = 10 : 1);

MS (FAB, Pos.) : 542 (M + H)<sup>+</sup>.

Example 4(6)

N-[4,5-dimethyl-2-[2-methoxy-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isopropyl-(5-methyl-2-furyl)sulfonylamide

[0285]



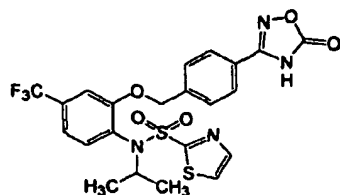
TLC: Rf 0.44 (dichloromethane: methanol = 19 : 1);

NMR:  $\delta$  7.68 (d, J = 8.1 Hz, 1H), 7.35 (dd, J = 8.1, 1.5 Hz, 1H), 7.24 (d, J = 1.5 Hz, 1H), 6.91 (d, J = 3.3 Hz, 1H), 6.77 (s, 1H), 6.72 (s, 1H), 6.11 (dd, J = 3.3, 0.6 Hz, 1H), 4.92 (d, J = 14.7 Hz, 1H), 4.83 (d, J = 14.7 Hz, 1H), 4.49 (m, 1H), 3.93 (s, 3H), 2.37 (s, 3H), 2.25 (s, 3H), 2.17 (s, 3H), 1.09 (d, J = 6.9 Hz, 3H), 1.07 (d, J = 6.9 Hz, 3H).

## Example 4(7)

N-[4-trifluoromethyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isopropyl-2-thiazolylsulfonamide

[0286]



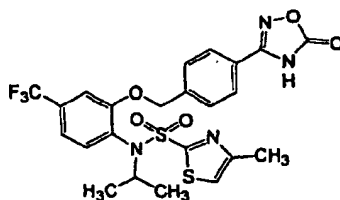
TLC: Rf 0.23 (n-hexane: ethyl acetate = 1 : 1);

NMR:  $\delta$  7.96 (d, J = 3.3 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 3.3 Hz, 1H), 7.34-7.22 (m, 3H), 5.19 (s, 2H), 4.68 (sept, J = 6.6 Hz, 1H), 1.15 and 1.14 (each d, J = 6.6 Hz, each 3H).

## Example 4(8)

N-[4-trifluoromethyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonamide

[0287]



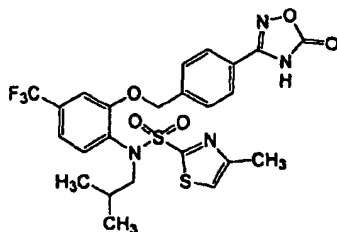
TLC: Rf 0.6 (chloroform : methanol : water = 8 : 2 : 0.2);

NMR:  $\delta$  7.82 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.32-7.24 (m, 3H), 7.11 (d, J = 0.9 Hz, 1H), 5.19 (s, 2H), 4.68 (quint, J = 6.6 Hz, 1H), 2.51 (d, J = 0.9 Hz, 3H), 1.14 (d, J = 6.6 Hz, 6H).

## Example 4(9)

N-[4-trifluoromethyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonamide

[0288]



TLC: Rf 0.60 (chloroform : methanol water = 8 : 2 : 0.2);

NMR:  $\delta$  7.83 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 7.8 Hz, 1H), 7.27 (m, 1H), 7.18 (d, J = 1.5 Hz,



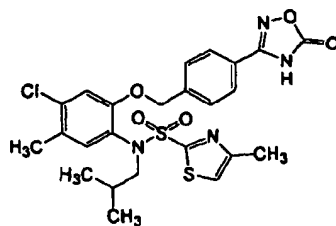
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1H), 7.04 (d, J = 0.6 Hz, 1H), 5.05 (br, 2H), 3.60 (d, J = 6.9 Hz, 2H), 2.38 (d, J = 0.6 Hz, 3H), 1.66 (sep, J = 6.9 Hz, 1H), 0.92 (d, J = 6.9 Hz, 6H).

## Example 4(10)

N-[4-chloro-5-methyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide

[0289]



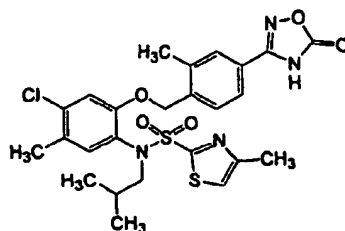
TLC : Rf 0.37 (chloroform : methanol = 19 : 1);

NMR :  $\delta$  10.89 (br, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.17 (s, 1H), 7.01 (s, 1H), 6.92 (s, 1H), 4.99 (br, 1H), 4.87 (br, 1H), 3.57 (br, 2H), 2.36 (s, 3H), 2.27 (s, 3H), 1.80-1.60 (m, 1H), 0.93 (d, J = 6.6 Hz, 6H).

## Example 4(11)

N-[4-chloro-5-methyl-2-[2-methyl-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide

[0290]



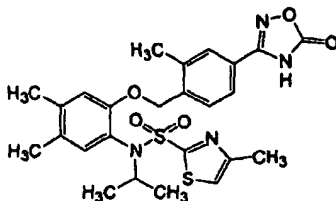
TLC : Rf 0.43 (ethyl acetate);

NMR(DMSO- $d_6$ ) :  $\delta$  7.67 (s, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.50 (s, 1H), 7.34 (s, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.21 (s, 1H), 5.06 (brs, 1H), 4.87 (brs, 1H), 3.45 (brs, 2H), 2.33 (s, 3H), 2.27 (s, 3H), 2.22 (s, 3H), 1.70-1.50 (m, 1H), 0.86 (brd, J = 6.3 Hz, 6H).

## Example 4(12)

N-[4,5-dimethyl-2-[2-methyl-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide

[0291]



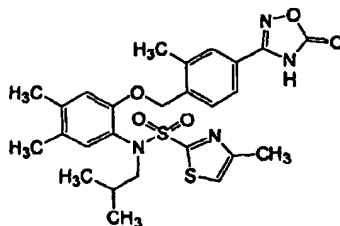
TLC: Rf 0.45 (chloroform: methanol = 19 : 1);

NMR :  $\delta$  10.56 (br, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.62 (s, 1H), 7.57 (dd, J = 8.1, 1.8 Hz, 1H), 7.07 (s, 1H), 6.83 (s, 1H), 6.77 (s, 1H), 4.98 (s, 2H), 4.75-4.60 (m, 1H), 2.49 (s, 3H), 2.39 (s, 3H), 2.25 (s, 3H), 2.16 (s, 3H), 1.14 (d, J = 6.6 Hz, 3H), 1.13 (d, J = 6.6 Hz, 3H).

## Example 4(13)

N-[4,5-dimethyl-2-[2-methyl-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide

[0292]



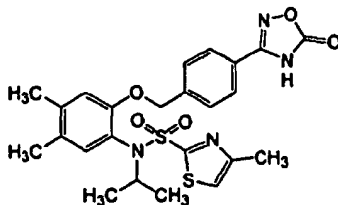
TLC: Rf 0.45 (chloroform: methanol = 19 : 1);

NMR :  $\delta$  10.95 (br, 1H), 7.62 (s, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.03 (s, 1H), 6.99 (s, 1H), 6.71 (s, 1H), 4.91 (br, 1H), 4.82 (br, 1H), 3.57 (br, 2H), 2.37 (s, 3H), 2.34 (s, 3H), 2.24 (s, 3H), 2.17 (s, 3H), 1.80-1.60 (m, 1H), 0.93 (br, 6H).

## Example 4(14)

N-[4,5-dimethyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide

[0293]



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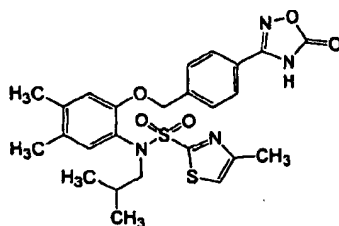
TLC : Rf 0.42 (chloroform : methanol = 10 : 1);

NMR :  $\delta$  7.77 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 0.9 Hz, 1H), 6.83 (s, 1H), 6.74 (s, 1H), 5.05 (d, J = 12.9 Hz, 1H), 5.00 (d, J = 12.9 Hz, 1H), 4.68 (m, 1H), 2.49 (d, J = 0.9 Hz, 3H), 2.24 (s, 3H), 2.15 (s, 3H), 1.15 (d, J = 6.6 Hz, 3H), 1.13 (d, J = 6.6 Hz, 3H).

Example 4(15)

N-[4,5-dimethyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isobutyl-(4-methyl-2-thiazolyl)sulfonylamide

[0294]



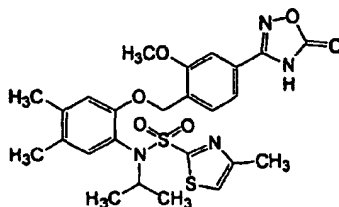
TLC : Rf 0.39 (chloroform : methanol = 10 : 1);

NMR :  $\delta$  7.78 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.03 (s, 1H), 6.97 (d, J = 0.9 Hz, 1H), 6.68 (s, 1H), 5.12-4.68 (m, 2H), 3.73-3.42 (m, 2H), 2.35 (d, J = 0.9 Hz, 3H), 2.23 (s, 3H), 2.17 (s, 3H), 1.69 (m, 1H), 1.03-0.86 (m, 6H).

Example 4(16)

N-[4,5-dimethyl-2-[2-methoxy-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isopropyl-(4-methyl-2-thiazolyl)sulfonylamide

[0295]



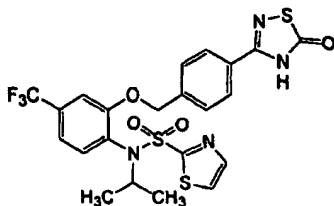
TLC : Rf 0.37 (dichloromethane : methanol = 19 : 1);

NMR :  $\delta$  7.63 (d, J = 7.8 Hz, 1H), 7.33 (dd, J = 7.8, 1.5 Hz, 1H), 7.30 (d, J = 1.5 Hz, 1H), 7.08 (brs, 1H), 6.83 (s, 1H), 6.76 (s, 1H), 5.02 (d, J = 14.4 Hz, 1H), 4.93 (d, J = 14.4 Hz, 1H), 4.69 (m, 1H), 3.93 (s, 3H), 2.49 (d, J = 1.2 Hz, 3H), 2.25 (s, 3H), 2.16 (s, 3H), 1.14 (d, J = 6.9 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H).

## Example 4(17)

N-[4-trifluoromethyl-2-[4-(5-oxo-1,2,4-thiadiazol-3-yl)phenylmethoxy]phenyl]-N-isopropyl-2-thiazolysulfonylamide

[0296]



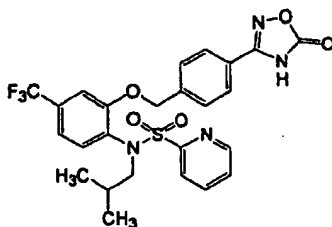
TLC : Rf 0.44 (n-hexane : ethyl acetate = 1 : 1);

NMR :  $\delta$  11.41 (brs, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 3.0 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 3.0 Hz, 1H), 7.34-7.20 (m, 3H), 5.16 (s, 2H), 4.69 (sept, J = 6.6 Hz, 1H), 1.15 (d, J = 6.6 Hz, 6H).

## Example 4(18)

N-[4-trifluoromethyl-2-[4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isobutyl-2-pyridylsulfonylamide

[0297]



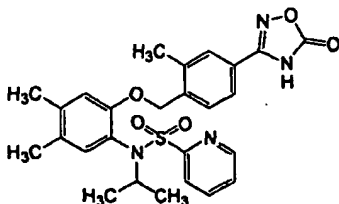
TLC : Rf 0.46 (chloroform : methanol = 9 : 1);

NMR(DMSO- $d_6$ ) :  $\delta$  8.60-8.50 (m, 1H), 7.90 (dt, J = 1.8, 7.8 Hz, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 7.5 Hz, 1H), 7.55-7.35 (m, 6H), 5.08 (brs, 2H), 3.52 (brd, J = 7.5 Hz, 2H), 1.60-1.40 (m, 1H), 0.83 (d, J = 6.6 Hz, 6H).

## Example 4(19)

N-[4,5-dimethyl-2-[2-methyl-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isopropyl-2-pyridylsulfonylamide

[0298]



TLC : Rf 0.33 (chloroform : methanol = 19 : 1);

NMR :  $\delta$  10.41 (br, 1H), 8.75-8.70 (m, 1H), 7.90 (dd, J = 7.8, 0.9 Hz, 1H), 7.80 (dt, J = 0.9, 7.8 Hz, 1H), 7.65-7.50 (m, 3H), 7.41 (ddd, J = 7.8, 4.8, 0.9 Hz, 1H), 6.78 (s, 1H), 6.72 (s, 1H), 4.87 (d, J = 13.4 Hz, 1H), 4.83 (d, J = 13.4 Hz, 1H),

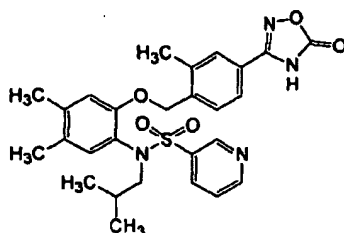
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4.75-4.60 (m, 1H), 2.34 (s, 3H), 2.25 (s, 3H), 2.13 (s, 3H), 1.10 (d, J = 6.6 Hz, 6H).

Example 4(20)

N-[4,5-dimethyl-2-[2-methyl-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isobutyl-3-pyridylsulfonamide

[0299]



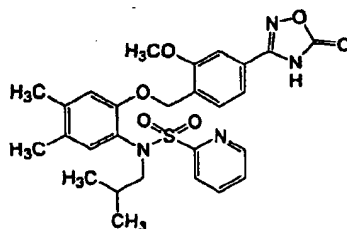
TLC : R<sub>f</sub> 0.30 (chloroform : methanol = 19 : 1);

NMR :  $\delta$  11.28 (br, 1H), 8.84 (d, J = 1.8 Hz, 1H), 8.49 (dd, J = 4.8, 1.8 Hz, 1H), 7.87 (dt, J = 8.1, 1.8 Hz, 1H), 7.62 (s, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.19 (dd, J = 8.1, 4.8 Hz, 1H), 7.16 (s, 1H), 6.97 (d, J = 7.8 Hz, 1H), 6.69 (s, 1H), 4.82 (br, 1H), 4.62 (br, 1H), 3.53 (br, 1H), 3.34 (br, 1H), 2.30 (s, 3H), 2.27 (s, 3H), 2.22 (s, 3H), 1.80-1.60 (m, 1H), 1.00 (br, 3H), 0.87 (br, 3H).

Example 4(21)

N-[4,5-dimethyl-2-[2-methoxy-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isobutyl-2-pyridylsulfonamide

[0300]



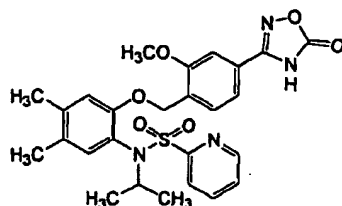
TLC: R<sub>f</sub> 0.36 (dichloromethane: methanol = 10 : 1);

MS (FAB, Pos.): 539 (M + H)<sup>+</sup>.

## Example 4(22)

N-(4,5-dimethyl-2-[2-methoxy-4-(5-oxo-1,2,4-oxadiazol-3-yl)phenylmethoxy]phenyl]-N-isopropyl-2-pyridylsulfonamide

[0301]



TLC : R<sub>f</sub> 0.37 (dichloromethane : methanol = 19 : 1);

NMR :  $\delta$  8.73 (ddd, J = 4.8, 1.5, 0.9 Hz, 1H), 7.91 (ddd, J = 7.8, 1.2, 0.9 Hz, 1H), 7.82 (ddd, J = 7.8, 7.8, 1.5 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.43 (ddd, J = 7.8, 4.8, 1.2 Hz, 1H), 7.32 (dd, J = 7.8, 1.5 Hz, 1H), 7.26 (m, 1H), 6.76 (s, 1H), 6.72 (s, 1H), 4.88 (d, J = 14.1 Hz, 1H), 4.78 (d, J = 14.1 Hz, 1H), 4.71 (in, 1H), 3.91 (s, 3H), 2.24 (s, 3H), 2.13 (s, 3H), 1.10 (d, J = 6.6 Hz, 3H), 1.09 (d, J = 6.6 Hz, 3H).

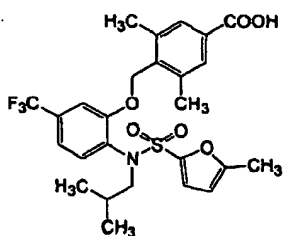
Example 5(1) ~ Example 5(63)

[0302] By the same procedure as described in reference examples 1 ~ 3 and example 2, the compounds of the present invention having the following physical data were obtained.

Example 5(1)

3,5-dimethyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-5-trifluoromethylphenoxy]benzoic acid

[0303]



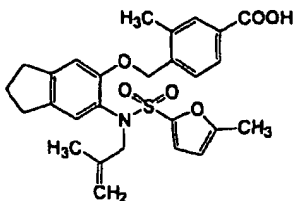
TLC R<sub>f</sub> 0.49 (chloroform : methanol = 10 : 1);

NMR :  $\delta$  7.82 (s, 2H), 7.40-7.20 (m, 3H), 6.70 (d, J = 3.3 Hz, 1H), 6.00-5.95 (m, 1H), 5.07 (s, 2H), 3.35 (d, J = 7.5 Hz, 2H), 2.43 (s, 6H), 2.19 (s, 3H), 1.60-1.45 (m, 1H), 0.79 (d, J = 6.6 Hz, 6H).

## Example 5(2)

3-methyl-4-[6-[N-(5-methyl-2-furylsulfonyl)-N-(2-methyl-2-propenyl)amino]indan-5-yloxymethyl]benzoic acid

[0304]



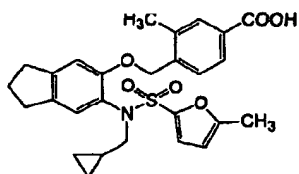
TLC : Rf 0.54 (chloroform : methanol = 9 : 1);

NMR(DMSO- $d_6$ ) :  $\delta$  7.80-7.70 (m, 2H), 7.37 (d, J = 7.8 Hz, 1H), 7.05 (s, 1H), 6.99 (s, 1H), 6.87 (d, J = 3.3 Hz, 1H), 6.17 (d, J = 3.3 Hz, 1H), 4.99 (br, 2H), 4.72 (s, 2H), 4.13 (br, 2H), 2.83 (t, J = 7.4 Hz, 2H), 2.77 (t, J = 7.4 Hz, 2H), 2.32 (s, 3H), 2.08 (s, 3H), 2.05-1.90 (m, 2H), 1.65 (s, 3H).

## Example 5(3)

4-[6-[N-cyclopropylmethyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxymethyl]-3-methylbenzoic acid

[0305]



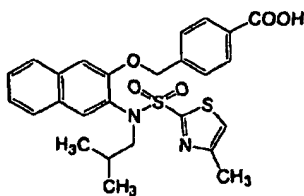
TLC : Rf 0.54 (chloroform : methanol = 9 : 1);

NMR(DMSO- $d_6$ ) :  $\delta$  7.77 (s, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.09 (s, 1H), 7.02 (s, 1H), 6.85 (d, J = 3.3 Hz, 1H), 6.20-6.15 (m, 1H), 5.01 (br, 2H), 3.41 (br, 2H), 2.86 (t, J = 7.4 Hz, 2H), 2.79 (t, J = 7.4 Hz, 2H), 2.32 (s, 3H), 2.10 (s, 3H), 2.10-1.95 (m, 2H), 0.90-0.70 (m, 1H), 0.35-0.25 (m, 2H), 0.05-(-0.05) (m, 2H).

## Example 5(4)

4-[3-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]naphthalen-2-yloxymethyl] benzoic acid

[0306]



TLC : Rf 0.55 (ethyl acetate : methanol = 9 : 1);

NMR :  $\delta$  8.14 (d, J = 8.4 Hz, 2H), 7.85 (s, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.51-7.37 (m, 4H),

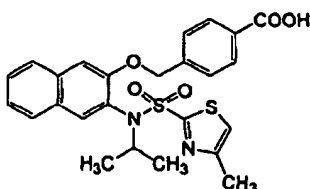
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7.18 (s, 1H), 6.93 (s, 1H), 5.17 and 4.96 (each br-m, total 2H), 3.85-3.62 (br-m, 2H), 2.34 (s, 3H), 1.82-1.69 (m, 1H), 0.97 (br-s, 6H).

Example 5(5)

4-[3-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]naphthalen-2-yloxymethyl] benzoic acid

[0307]



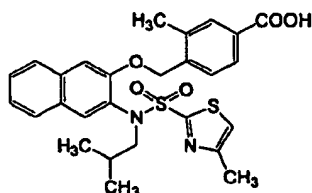
TLC : Rf 0.55 (ethyl acetate : methanol = 9 : 1);

NMR :  $\delta$  8.15 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 9.0 Hz, 2H), 7.61 (s, 1H), 7.60 (d, J = 9.0 Hz, 2H), 7.51-7.46 (m, 1H), 7.44-7.35 (m, 1H), 7.24 (s, 1H), 7.03 (s, 1H), 5.24 (s, 2H), 4.84-4.75 (m, 1H), 2.52 (s, 3H), 1.26 (d, J = 6.6 Hz, 3H), 1.17 (d, J = 6.6 Hz, 3H).

Example 5(6)

4-[3-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]naphthalen-2-yloxymethyl]-3-methylbenzoic acid

[0308]



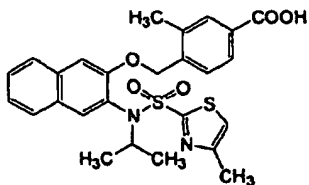
TLC: Rf 0.63 (ethyl acetate: methanol = 9 : 1);

NMR :  $\delta$  7.98-7.96 (m, 2H), 7.84 (s, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.52-7.47 (m, 1H), 7.42-7.37 (m, 2H), 7.21 (s, 1H), 6.95 (s, 1H), 5.10 and 4.96 (each br-m, total 2H), 3.84-3.60 (br-m, 2H), 2.41 (s, 3H), 2.34 (s, 3H), 1.82-1.68 (m, 1H), 0.96 (brs, 6H)

Example 5(7)

4-[3-[N-isopropyl-N-[2-(4-methylthiazolyl)sulfonyl]amino]naphthalen-2-yloxymethyl]-3-methylbenzoic acid

[0309]



TLC : Rf 0.56 (ethyl acetate : methanol = 9 : 1);



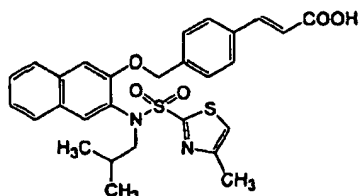
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NMR :  $\delta$  8.00-7.97 (m, 2H), 7.76-7.65 (m, 3H), 7.61 (s, 1H), 7.52-7.47 (m, 1H), 7.40-7.35 (m, 1H), 7.26 (s, 1H), 7.04 (s, 1H), 5.22 (d, J = 15.0 Hz, 1H), 5.17 (d, J = 15.0 Hz, 1H), 4.83-4.73 (m, 1H), 2.53 (s, 3H), 2.46 (s, 3H), 1.25 (d, J = 6.6 Hz, 3H), 1.16 (d, J = 6.6 Hz, 3H).

## 5 Example 5(8)

4-[3-(N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino)naphthalen-2-yloxymethyl] cinnamic acid

[0310]



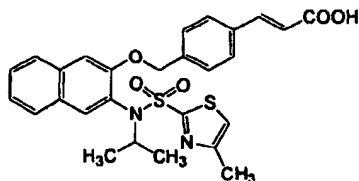
20 TLC : Rf 0.67 (ethyl acetate : methanol = 9 : 1);

NMR :  $\delta$  7.84-7.69 (m, 4H), 7.58 (d, J = 8.1 Hz, 2H), 7.51-7.45 (m, 1H), 7.41-7.35 (m, 3H), 7.18 (s, 1H), 6.93 (s, 1H), 6.49 (d, J = 16.2 Hz, 1H), 5.02 and 4.91 (each br-m, total 2H), 3.84-3.62 (brm, 2H), 2.33 (s, 3H), 1.82-1.68 (m, 1H), 0.91 (br-s, 6H).

## 25 Example 5(9)

4-[3-(N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino)naphthalen-2-yloxymethyl] cinnamic acid

[0311]



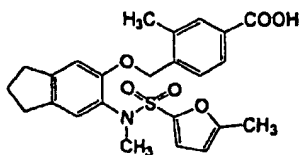
35 TLC: Rf 0.61 (ethyl acetate: methanol = 9 : 1);

40 NMR :  $\delta$  7.80 (d, J = 16.9 Hz, 1H), 7.71 (d, J = 8.7 Hz, 2H), 7.61-7.46 (m, 6H), 7.39-7.34 (m, 1H), 7.24 (s, 1H), 7.03 (s, 1H), 6.48 (d, J = 16.9 Hz, 1H), 5.19 (s, 2H), 4.85-4.72 (m, 1H), 2.51 (s, 3H), 1.25 (d, J = 6.6 Hz, 3H), 1.16 (d, J = 6.6 Hz, 3H).

## 45 Example 5(10)

3-methyl-4-[6-[N-methyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxymethyl]benzoic acid

[0312]



55 TLC : Rf 0.58 (chloroform : methanol = 9 : 1);

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NMR(DMSO- $d_6$ ) :  $\delta$  7.77 (s, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.09 (s, 1H), 6.99 (s, 1H), 6.90 (d, J = 3.3 Hz, 1H), 6.25-6.15 (m, 1H), 5.02 (s, 2H), 3.15 (s, 3H), 2.84 (t, J = 7.4 Hz, 2H), 2.78 (t, J = 7.4 Hz, 2H), 2.32 (s, 3H), 2.12 (s, 3H), 2.10-1.95 (m, 2H).

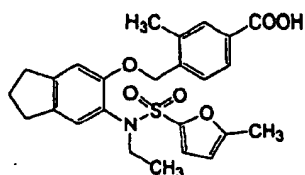
5 Example 5(11)

4-[6-[N-ethyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxymethyl]-3-methylbenzoic acid

[0313]

10

15



TLC: R<sub>f</sub> 0.59 (chloroform methanol = 9 : 1);

20 NMR(DMSO- $d_6$ ) :  $\delta$  7.77 (s, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.10 (s, 1H), 6.95 (s, 1H), 6.86 (d, J = 3.3 Hz, 1H), 6.16 (d, J = 3.3 Hz, 1H), 5.01 (br, 2H), 3.58 (br, 2H), 2.86 (t, J = 7.4 Hz, 2H), 2.79 (t, J = 7.4 Hz, 2H), 2.32 (s, 3H), 2.10 (s, 3H), 2.10-1.95 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H).

25 Example 5(12)

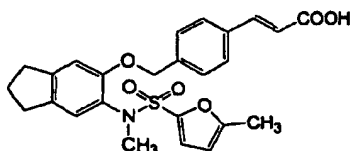
25

4-[6-[N-methyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxymethyl]cinnamic acid

[0314]

30

35



TLC : R<sub>f</sub> 0.53 (chloroform : methanol = 9 : 1);

40 NMR :  $\delta$  7.77 (d, J = 15.9 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.14 (s, 1H), 6.80 (s, 1H), 6.79 (d, J = 3.6 Hz, 1H), 6.47 (d, J = 15.9 Hz, 1H), 5.97 (d, J = 3.6 Hz, 1H), 4.98 (s, 2 H), 3.31 (s, 3H), 2.90-2.80 (m, 4H), 2.17 (s, 3H), 2.08 (quint, J = 7.5 Hz, 2H).

Example 5(13)

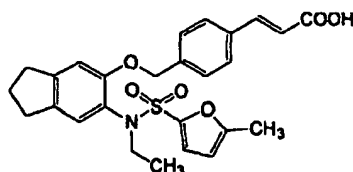
45

4-[6-[N-ethyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxymethyl]cinnamic acid

[0315]

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TLC: R<sub>f</sub> 0.53 (chloroform: methanol = 9 : 1);

NMR :  $\delta$  7.77 (d, J = 16.2 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.08 (s, 1H), 6.80 (s, 1H), 6.75 (d, J = 3.3 Hz, 1H), 6.47 (d, J = 16.2 Hz, 1H), 5.94 (d, J = 3.3 Hz, 1H), 4.97 (s, 2 H), 3.82-3.65 (m, 2H), 2.90-2.80 (m,

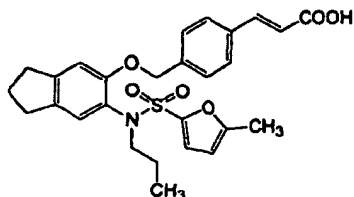
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4H), 2.15 (s, 3H), 2.08 (quint, J = 7.2 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H).

Example 5(14)

4-[6-[N-(5-methyl-2-furylsulfonyl)-N-propylamino]indan-5-yloxymethyl]cinnamic acid

[0316]



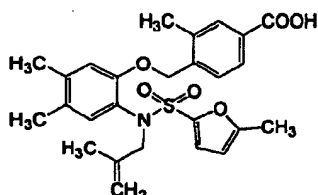
TLC: Rf 0.54 (chloroform: methanol = 9 : 1);

NMR :  $\delta$  7.78 (d, J = 15.9 Hz, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.08 (s, 1H), 6.79 (s, 1H), 6.74 (d, J = 3.3 Hz, 1H), 6.46 (d, J = 15.9 Hz, 1H), 5.94 (brd, J = 3.3 Hz, 1H), 4.97 (br s, 2H), 3.65-3.61 (m, 2H), 2.90-2.80 (m, 4H), 2.15 (s, 3H), 2.08 (quint, J = 7.5 Hz, 2H), 1.53 (sext, J = 7.2 Hz, 2H), 0.89 (t, J = 7.2 Hz, 3H).

Example 5(15)

4-[4,5-dimethyl-2-[N-(5-methyl-2-furylsulfonyl)-N-(2-methyl-2-propenyl)amino]phenoxy methyl]-3-methylbenzoic acid

[0317]



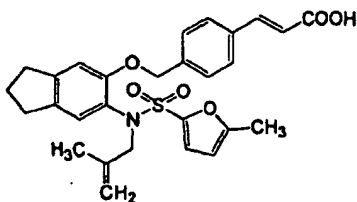
TLC : Rf 0.45 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  8.00-7.93 (m, 2H), 7.44 (d, J = 8.1 Hz, 1H), 7.02 (s, 1H), 6.75 (d, J = 3.3 Hz, 1H), 6.69 (s, 1H), 5.96 (m, 1H), 4.94 (s, 2H), 4.77 (s, 2H), 4.27 (s, 2H), 2.38 (s, 3H), 2.22 (s, 3H), 2.18 (s, 3H), 2.12 (s, 3H), 1.78 (s, 3H).

Example 5(16)

4-[6-[N-(5-methyl-2-furylsulfonyl)-N-(2-methyl-2-propenyl)amino]indan-5-yloxymethyl] cinnamic acid

[0318]



TLC : Rf 0.61 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.78 (d, J = 15.9 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.09 (s, 1H), 6.76 (s, 1H), 6.74

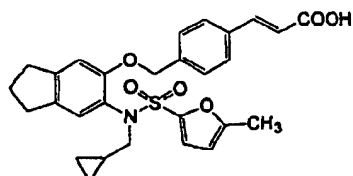
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(d, J = 3.0 Hz, 1H), 6.47 (d, J = 15.9 Hz, 1H), 5.94 (d, J = 3.0 Hz, 1H), 4.95 (brs, 2H), 4.77 (s, 2H), 4.38-4.18 (m, 2H), 2.90-2.75 (m, 4H), 2.14 (s, 3H), 2.07 (quint, J = 7.5 Hz, 2H), 1.78 (s, 3H).

Example 5(17)

4-[6-[N-cyclopropylmethyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxymethyl] cinnamic acid

[0319]



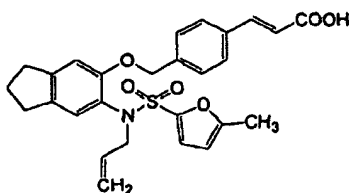
TLC : Rf 0.51 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.79 (d, J = 15.9 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.15 (s, 1H), 6.79 (s, 1H), 6.74 (d, J = 3.3 Hz, 1H), 6.47 (d, J = 15.9 Hz, 1H), 5.94 (d, J = 3.3 Hz, 1H), 4.97 (brs, 2H), 3.65-3.50 (m, 2H), 2.92-2.70 (m, 4H), 2.15 (s, 3H), 2.08 (quint, J = 7.5 Hz, 2H), 1.00-0.85 (m, 1H), 0.45-0.36 (m, 2H), 0.20-0.05 (m, 2H).

Example 5(18)

4-[6-[N-(5-methyl-2-furylsulfonyl)-N-(2-propenyl)amino]indan-5-yloxymethyl]cinnamic acid

[0320]



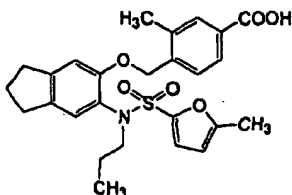
TLC : Rf 0.57 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.79 (d, J = 15.9 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.07 (s, 1H), 6.78 (s, 1H), 6.76 (d, J = 3.3 Hz, 1H), 6.47 (d, J = 15.9 Hz, 1H), 5.96 (d, J = 3.3 Hz, 1H), 5.96-5.77 (m, 1H), 5.13-5.03 (m, 2H), 4.97 (s, 2H), 4.42-4.20 (m, 2H), 2.90-2.80 (m, 4H), 2.16 (s, 3H), 2.07 (quint, J = 7.5 Hz, 2H).

Example 5(19)

3-methyl-4-[6-[N-(5-methyl-2-furylsulfonyl)-N-propylamino]indan-5-yloxymethyl]benzoic acid

[0321]



TLC: Rf 0.40 (chloroform: methanol = 10 : 1);

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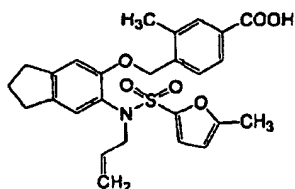
NMR :  $\delta$  7.95 (d, J = 7.8 Hz, 1H), 7.93 (s, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.10 (s, 1H), 6.81 (s, 1H), 6.75 (d, J = 3.3 Hz, 1H), 5.95 (dd, J = 3.3, 0.9 Hz, 1H), 4.96 (s, 2H), 3.76-3.47 (m, 2H), 2.92-2.82 (m, 4H), 2.37 (s, 3H), 2.13 (s, 3H), 2.15-2.03 (m, 2H), 1.60-1.47 (m, 2H), 0.89 (t, J = 7.5 Hz, 3H).

## 5 Example 5(20)

3-methyl-4-[6-[N-(5-methyl-2-furylsulfonyl)-N-(2-propenyl)amino]indan-5-yloxymethyl] benzoic acid

[0322]

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20 TLC: Rf 0.41 (chloroform: methanol = 10 : 1);

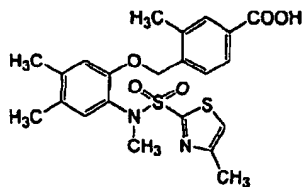
NMR :  $\delta$  7.95 (d, J = 7.8 Hz, 1H), 7.94 (s, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.08 (s, 1H), 6.80 (s, 1H), 6.78 (d, J = 3.3 Hz, 1H), 5.97 (d, J = 3.3 Hz, 1H), 5.85 (m, 1H), 5.10 (dd, J = 16.8, 1.2 Hz, 1H), 5.05 (dd, J = 9.9, 1.2 Hz, 1H), 4.97 (s, 2H), 4.43-4.18 (m, 2H), 2.91-2.81 (m, 4H), 2.37 (s, 3H), 2.15 (s, 3H), 2.13-2.03 (m, 2H).

## 25 Example 5(21)

4-[4,5-dimethyl-2-[N-methyl-N-(4-methyl-2-thiazolylsulfonyl)amino]phenoxyethyl]-3-methylbenzoic acid

[0323]

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40 TLC Rf 0.49 (dichloromethane : methanol = 10 : 1);

NMR :  $\delta$  7.94-7.90 (m, 2H), 7.31 (d, J = 9.0 Hz, 1H), 7.13 (s, 1H), 6.94 (m, 1H), 6.73 (s, 1H), 4.88 (s, 2H), 3.42 (s, 3H), 2.35 (s, 3H), 2.34 (d, J = 0.9 Hz, 3H), 2.24 (s, 3H), 2.19 (s, 3H).

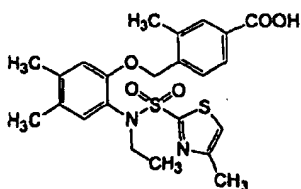
## 45 Example 5(22)

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4-[4,5-dimethyl-2-[N-ethyl-N-(4-methyl-2-thiazolylsulfonyl)amino]phenoxyethyl]-3-methylbenzoic acid

[0324]

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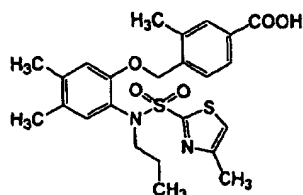
TLC : Rf 0.49 (dichloromethane : methanol = 10 : 1);

NMR :  $\delta$  7.96-7.90 (m, 2H), 7.32 (d, J = 8.1 Hz, 1H), 7.06 (s, 1H), 6.90 (m, 1H), 6.74 (s, 1H), 4.87 (brs, 2H), 3.85 (br, 2H), 2.34 (s, 3H), 2.32 (d, J = 0.9 Hz, 3H), 2.25 (s, 3H), 2.19 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H).

## 5 Example 5(23)

4-[4,5-dimethyl-2-[N-(4-methyl-2-thiazolylsulfonyl)-N-propylamino]phenoxy methyl]-3-methylbenzoic acid

[0325]



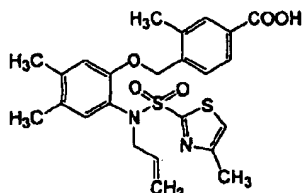
TLC : Rf 0.49(dichloromethane : methanol = 10 : 1);

NMR(DMSO- $d_6$ ) :  $\delta$  12.88 (s, 1H), 7.78-7.72 (m, 2H), 7.49 (m, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.03 (s, 1H), 6.95 (s, 1H), 4.88 (br, 2H), 3.59 (br, 2H), 2.28 (s, 3H), 2.22 (s, 3H), 2.18 (s, 3H), 2.13 (s, 3H), 1.44-1.35 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H).

## 25 Example 5(24)

4-[4,5-dimethyl-2-[N-(4-methyl-2-thiazolylsulfonyl)-N-(2-propenyl)amino]phenoxy methyl]-3-methylbenzoic acid

[0326]



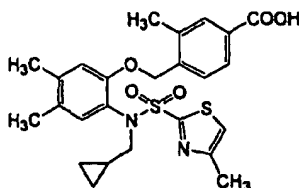
40 TLC: Rf 0.49 (dichloromethane: methanol = 10 : 1);

NMR(DMSO- $d_6$ ) :  $\delta$  12.88 (s, 1H), 7.78-7.72 (m, 2H), 7.50 (s, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.01 (s, 1H), 6.95 (s, 1H), 5.74 (m, 1H), 5.09 (d, J = 17.1 Hz, 1H), 5.04 (d, J = 9.9 Hz, 1H), 4.89 (br, 2H), 4.27 (br, 2H), 2.29 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H), 2.12 (s, 3H).

## 45 Example 5(25)

4-[2-[N-cyclopropylmethyl-N-(4-methyl-2-thiazolylsulfonyl)amino-4,5-dimethyl]phenoxy methyl] 3-methylbenzoic acid

[0327]



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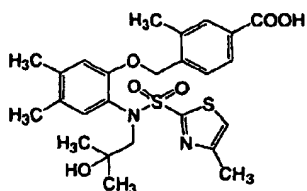
TLC : Rf 0.49 (dichloromethane : methanol = 10 : 1);

NMR(DMSO-d<sub>6</sub>) :  $\delta$  12.87 (br, 1H), 7.78-7.72 (m, 2H), 7.48 (s, 1H), 7.25 (d, J = 7.5 Hz, 1H), 7.03 (s, 1H), 7.00 (s, 1H), 4.90 (br, 2H), 3.45 (br, 2H), 2.27 (s, 3H), 2.23 (s, 3H), 2.17 (s, 3H), 2.14 (s, 3H), 0.82 (m, 1H), 0.38-0.30 (m, 2H), 0.10-0.02 (m, 2H).

Example 5(26)

4-[4,5-dimethyl-2-[N-(2-hydroxy-2-methylpropyl)-N-(4-methyl-2-thiazolylsulfonyl)amino] phenoxyethyl]-3-methylbenzoic acid

[0328]



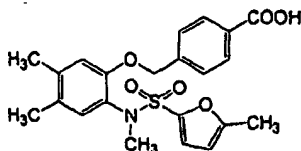
TLC : Rf 0.49 (dichloromethane : methanol = 10 : 1);

NMR :  $\delta$  7.99-7.94 (m, 2H), 7.47 (d, J = 8.1 Hz, 1H), 7.04 (m, 1H), 6.79 (s, 1H), 6.77 (s, 1H), 5.06 (d, J = 12.3 Hz, 1H), 4.95 (d, J = 12.3 Hz, 1H), 3.95 (d, J = 15.3 Hz, 1H), 3.73 (d, J = 15.3 Hz, 1H), 2.420 (s, 3H), 2.417 (s, 3H), 2.23 (s, 3H), 2.11 (s, 3H), 1.25 (s, 3H), 1.21 (s, 3H).

Example 5(27)

4-[4,5-dimethyl-2-[N-methyl-N-(5-methyl-2-furylsulfonyl)amino]phenoxyethyl]benzoic acid

[0329]



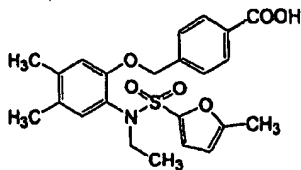
TLC : Rf 0.46 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  8.11 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.08 (s, 1H), 6.79 (d, J = 3.3 Hz, 1H), 6.71 (s, 1H), 5.99-5.95 (m, 1H), 5.03 (s, 2H), 3.31 (s, 3H), 2.22 (s, 3H), 2.18 (s, 3H), 2.16 (s, 3H).

Example 5(28)

4-[4,5-dimethyl-2-[N-ethyl-N-(5-methyl-2-furylsulfonyl)amino]phenoxyethyl]benzoic acid

[0330]



TLC : Rf 0.41 (chloroform : methanol = 9 : 1);

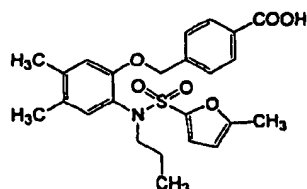
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NMR :  $\delta$  8.10 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.01 (s, 1H), 6.76 (d, J = 3.3 Hz, 1H), 6.71 (s, 1H), 5.96-5.93 (m, 1H), 5.02 (s, 2H), 3.83-3.65 (m, 2H), 2.23 (s, 3H), 2.18 (s, 3H), 2.14 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H).

Example 5(29)

4-[4,5-dimethyl-2-[N-(5-methyl-2-furylsulfonyl)-N-propylamino]phenoxy]benzoic acid

[0331]



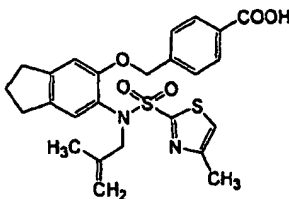
TLC: Rf 0.43 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  8.11 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.02 (s, 1H), 6.74 (d, J = 3.0 Hz, 1H), 6.70 (s, 1H), 5.96-5.93 (m, 1H), 5.01 (s, 2H), 3.75-3.53 (m, 2H), 2.22 (s, 3H), 2.18 (s, 3H), 2.14 (s, 3H), 1.60-1.46 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H).

Example 5(30)

4-[6-[N-(2-methyl-2-propenyl)-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxy]benzoic acid

[0332]



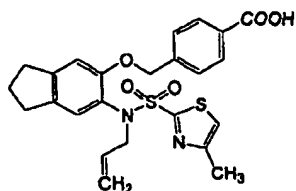
TLC: Rf 0.36 (dichloromethane : methanol = 19 : 1);

NMR :  $\delta$  8.11 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 7.14 (s, 1H), 6.92 (brs, 1H), 6.74 (s, 1H), 5.10-4.70 (brs, 2H), 4.80 (brs, 2H), 4.60-4.20 (brs, 2H), 2.88-2.82 (m, 4H), 2.32 (d, J = 0.9 Hz, 3H), 2.07 (m, 2H), 1.83 (s, 3H).

Example 5(31)

4-[6-[N-(4-methyl-2-thiazolylsulfonyl)-N-(2-propenyl)amino]indan-5-yloxy]benzoic acid

[0333]



TLC : Rf 0.34 (dichloromethane : methanol = 19 : 1);



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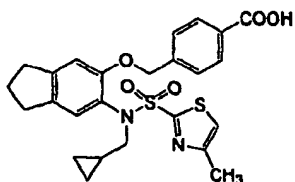
NMR :  $\delta$  8.11 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 7.13 (s, 1H), 6.93 (brs, 1H), 6.76 (s, 1H), 5.89 (ddt, J = 17.1, 10.2, 6.3 Hz, 1H), 5.17-5.06 (m, 2H), 4.92 (brs, 2H), 4.70-4.10 (brs, 2H), 2.89-2.83 (m, 4H), 2.34 (d, J = 0.9 Hz, 3H), 2.08 (m, 2H).

5 Example 5(32)

4-[6-[N-cyclopropylmethyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl] benzoic acid

[0334]

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15

20 TLC : Rf 0.36 (dichloromethane : methanol = 19 : 1);

NMR :  $\delta$  8.10 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 7.22 (s, 1H), 6.89 (brs, 1H), 6.78 (s, 1H), 5.10-4.70 (m, 2H), 3.90-3.50 (m, 2H), 2.90-2.85 (m, 4H), 2.32 (d, J = 0.9 Hz, 3H), 2.09 (m, 2H), 1.00 (m, 1H), 0.43 (m, 2H), 0.20 (brs, 2H).

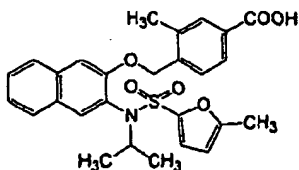
Example 5(33)

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4-[3-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]naphthalen-2-yloxymethyl]-3-methylbenzoic acid

[0335]

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TLC : Rf 0.52 (chloroform : methanol = 9 : 1);

40 NMR(DMSO- $d_6$ ) :  $\delta$  7.92-7.80 (m, 3H), 7.77 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.63 (s, 1H), 7.60 (s, 1H), 7.57-7.50 (m, 1H), 7.45-7.36 (m, 1H), 6.95 (d, J = 3.3 Hz, 1H), 6.29 (d, J = 3.3 Hz, 1H), 5.26 and 5.24 (each d, J = 13.5 Hz, each 1H), 4.34 (sept, J = 6.6 Hz, 1H), 2.42 (s, 3H), 2.34 (s, 3H), 1.06 and 1.00 (each d, J = 6.6 Hz, each 3H).

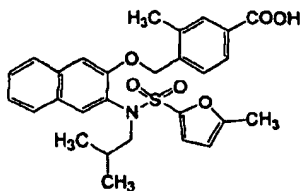
Example 5(34)

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4-[3-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]naphthalen-2-yloxymethyl]-3-methylbenzoic acid

[0336]

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TLC: Rf 0.50 (chloroform : methanol = 9 : 1);

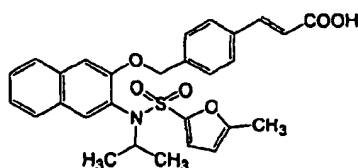
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NMR(DMSO- $d_6$ ) :  $\delta$  7.88 (d, J = 7.8 Hz, 1H), 7.86-7.74 (m, 4H), 7.59 (s, 1H), 7.56-7.36 (m, 3H), 6.86 (d, J = 3.3 Hz, 1H), 6.19 (d, J = 3.3 Hz, 1H), 5.40-4.90 (br, 2H), 3.47 (brd, J = 6.9 Hz, 2H), 2.39 (s, 3H), 2.12 (s, 3H), 1.65-1.50 (m, 1H), 0.83 (brd, J = 6.3 Hz, 6H).

Example 5(35)

4-[3-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]naphthalen-2-yloxymethyl]cinnamic acid

[0337]



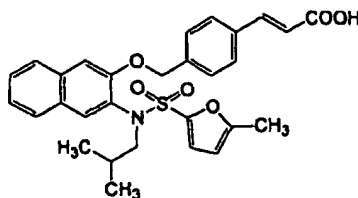
TLC : Rf 0.45 (chloroform : methanol = 9:1);

NMR(DMSO- $d_6$ ) :  $\delta$  7.87 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.67-7.46 (m, 6H), 7.44-7.34 (m, 1H), 6.94 (d, J = 3.3 Hz, 1H), 6.56 (d, J = 15.9 Hz, 1H), 6.28 (d, J = 3.3 Hz, 1H), 5.27 and 5.21 (each d, J = 13.2 Hz, each 1H), 4.36 (sept, J = 6.6 Hz, 1H), 2.33 (s, 3H), 1.08 and 1.03 (each d, J = 6.6 Hz, each 3H).

Example 5(36)

4-[3-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]naphthalen-2-yloxymethyl]cinnamic acid

[0338]



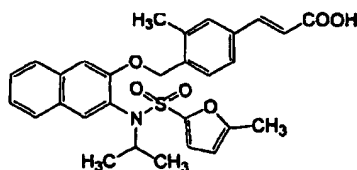
TLC : Rf 0.45 (chloroform : methanol = 9 : 1);

NMR(DMSO- $d_6$ ) :  $\delta$  7.88 (d, J = 8.4 Hz, 1H), 7.81 (s, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 7.8 Hz, 2H), 7.61 (d, J = 15.9 Hz, 1H), 7.55-7.34 (m, 2H), 7.50 (s, 1H), 7.44 (d, J = 7.8 Hz, 2H), 6.82 (d, J = 3.6 Hz, 1H), 6.56 (d, J = 15.9 Hz, 1H), 6.16 (d, J = 3.6 Hz, 1H), 5.40-4.90 (br, 2H), 3.49 (d, J = 6.6 Hz, 2H), 2.13 (s, 3H), 1.64-1.48 (m, 1H), 0.85 (d, J = 6.6 Hz, 6H).

Example 5(37)

4-[3-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]naphthalen-2-yloxymethyl]-3-methylcinnamic acid

[0339]



TLC : Rf 0.46 (chloroform : methanol = 9 : 1) ;

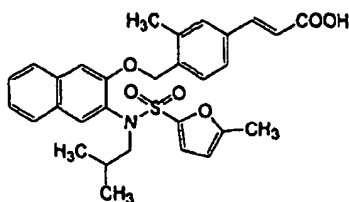
# EP 1 369 129 A1

NMR(DMSO- $d_6$ ) :  $\delta$  7.87 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.64-7.48 (m, 7H), 7.44-7.36 (m, 1H), 6.93 (d, J = 3.6 Hz, 1H), 6.54 (d, J = 15.9 Hz, 1H), 6.29 (d, J = 3.6 Hz, 1H), 5.23 and 5.18 (each d, J = 14.4 Hz, each 1H), 4.33 (sept, J = 6.6 Hz, 1H), 2.39 (s, 3H), 2.34 (s, 3H), 1.06 and 1.00 (each d, J = 6.6 Hz, each 3H).

## 5 Example 5(38)

4-[3-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]naphthalen-2-yloxymethyl]-3-methylcinnamic acid

[0340]



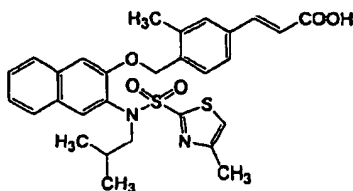
TLC : Rf 0.46 (chloroform : methanol = 9 : 1);

NMR(DMSO- $d_6$ ) :  $\delta$  7.88 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.78 (s, 1H), 7.62-7.47 (m, 5H), 7.44-7.35 (m, 2H), 6.84 (d, J = 3.6 Hz, 1H), 6.54 (d, J = 16.2 Hz, 1H), 6.20 (d, J = 3.6 Hz, 1H), 5.35-4.90 (br, 2H), 3.47 (d, J = 7.2 Hz, 2H), 2.35 (s, 3H), 2.14 (s, 3H), 1.63-1.49 (m, 1H), 0.83 (d, J = 6.3 Hz, 6H).

## Example 5(39)

4-[3-[N-isobutyl-N-[2-(4-methylthiazolyl)sulfonyl]amino]naphthalen-2-yloxymethyl]-3-methylbenzoic acid

[0341]



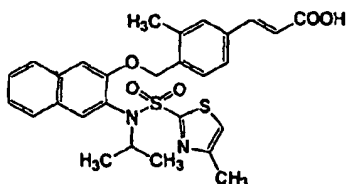
TLC : Rf 0.71 (ethyl acetate : methanol = 9 : 1);

NMR :  $\delta$  7.82-7.71 (m, 4H), 7.51-7.46 (m, 1H), 7.43-7.32 (m, 4H), 7.21 (s, 1H), 6.95 (s, 1H), 6.48 (d, J = 16.2 Hz, 1H), 5.04 and 4.91 (each br-m, total 2H), 3.83-3.60 (br-m, 2H), 2.38 (s, 3H), 2.34 (s, 3H), 1.81-1.67 (m, 1H), 0.95 (br-s, 6H).

Example 5(40)

4-[3-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]naphthalen-2-yloxymethyl]-3-methylbenzoic acid

[0342]



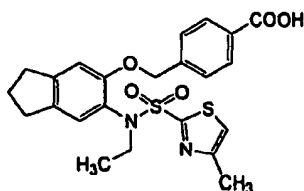
TLC : Rf 0.71 (ethyl acetate : methanol = 9 : 1);

NMR(DMSO- $d_6$ ) :  $\delta$  7.88-7.83 (m, 2H), 7.65-7.47 (m, 8H), 7.42-7.37 (m, 1H), 6.55 (d, J = 15.9 Hz, 1H), 5.16 (s, 2H), 4.62-4.49 (m, 1H), 2.42 (s, 3H), 2.36 (s, 3H), 1.13 (d, J = 6.6 Hz, 3H), 1.03 (d, J = 6.6 Hz, 3H).

Example 5(41)

4-[6-[N-ethyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]benzoic acid

[0343]



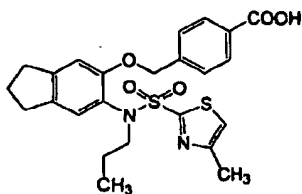
TLC : Rf 0.34 (dichloromethane : methanol = 19 : 1);

NMR :  $\delta$  8.10 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.14 (s, 1H), 6.90 (brs, 1H), 6.79 (s, 1H), 4.92 (m, 2H), 4.20-3.60 (m, 2H), 2.90-2.83 (m, 4H), 2.33 (s, 3H), 2.09 (m, 2H), 1.20 (t, J = 7.2 Hz, 3H).

Example 5(42)

4-[6-[N-(4-methyl-2-thiazolylsulfonyl)-N-propylamino]indan-5-yloxymethyl]benzoic acid

[0344]



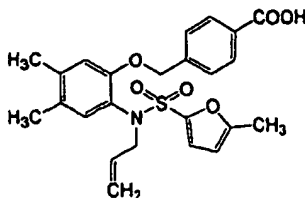
TLC : Rf 0.34 (dichloromethane : methanol = 19 : 1);

NMR :  $\delta$  8.11 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.15 (s, 1H), 6.90 (brs, 1H), 6.78 (s, 1H), 5.10-4.70 (m, 2H), 4.00-3.50 (m, 2H), 2.90-2.84 (m, 4H), 2.32 (s, 3H), 2.09 (m, 2H), 1.58 (m, 2H), 0.93 (t, J = 7.5 Hz, 3H).

## Example 5(43)

4-[4,5-dimethyl-2-[N-(5-methyl-2-furylsulfonyl)-N-(2-propenyl)amino]phenoxy]methyl] benzoic acid

[0345]



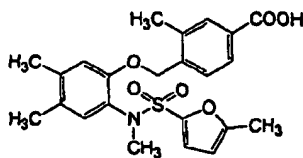
TLC : Rf 0.44 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  8.12 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.01 (s, 1H), 6.77 (d, J = 3.0 Hz, 1H), 6.68 (s, 1H), 5.99-5.94 (m, 1H), 5.92-5.75 (m, 1H), 5.16-5.03 (m, 2H), 5.02 (s, 2H), 4.42-4.20 (m, 2H), 2.21 (s, 3H), 2.17 (s, 3H), 2.15 (s, 3H).

## Example 5(44)

4-[4,5-dimethyl-2-[N-methyl-N-(5-methyl-2-furylsulfonyl)amino]phenoxy]methyl]-3-methylbenzoic acid

[0346]



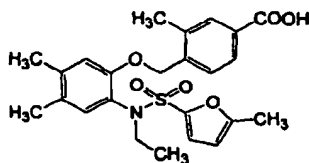
TLC : Rf 0.42 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.98-7.91 (m, 2H), 7.43 (d, J = 8.7 Hz, 1H), 7.08 (s, 1H), 6.79 (d, J = 3.3 Hz, 1H), 6.74 (s, 1H), 5.98 (m, 1H), 4.98 (s, 2H), 3.30 (s, 3H), 2.38 (s, 3H), 2.24 (s, 3H), 2.19 (s, 3H), 2.15 (s, 3H).

## Example 5(45)

4-[4,5-dimethyl-2-[N-ethyl-N-(5-methyl-2-furylsulfonyl)amino]phenoxy]methyl]-3-methylbenzoic acid

[0347]



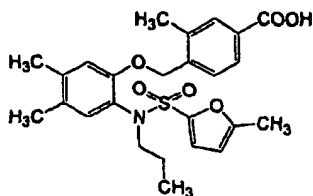
TLC: Rf 0.42 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.97-7.90 (m, 2H), 7.45 (d, J = 8.1 Hz, 1H), 7.01 (s, 1H), 6.76 (s, 1H), 6.75 (d, J = 3.3 Hz, 1H), 5.95 (m, 1H), 4.96 (s, 2H), 3.82-3.66 (br, 2H), 2.37 (s, 3H), 2.25 (s, 3H), 2.19 (s, 3H), 2.13 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H).

## Example 5(46)

4-[4,5-dimethyl-2-[N-(5-methyl-2-furylsulfonyl)-N-propylamino]phenoxy]methyl]-3-methylbenzoic acid

[0348]



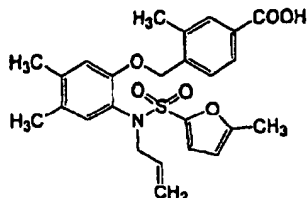
TLC: Rf 0.42 (chloroform : methanol = 9 : 1);

NMR:  $\delta$  7.98-7.90 (m, 2H), 7.45 (d, J = 8.1 Hz, 1H), 7.02 (s, 1H), 6.78-6.70 (m, 2H), 5.95 (m, 1H), 4.95 (s, 2H), 3.71-3.55 (br, 2H), 2.37 (s, 3H), 2.24 (s, 3H), 2.19 (s, 3H), 2.12 (s, 3H), 1.60-1.44 (m, 2H), 0.88 (t, J = 7.5 Hz, 3H).

## Example 5(47)

4-(4,5-dimethyl-2-[N-(5-methyl-2-furylsulfonyl)-N-(2-propenyl)amino]phenoxy]methyl]-3-methylbenzoic acid

[0349]



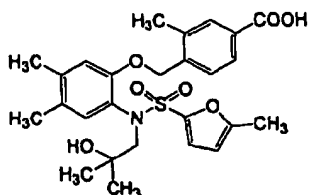
TLC : Rf 0.45 (chloroform : methanol = 9 : 1);

NMR:  $\delta$  7.98-7.90 (m, 2H), 7.45 (d, J = 8.1 Hz, 1H), 7.01 (s, 1H), 6.77 (d, J = 3.3 Hz, 1H), 6.71 (s, 1H), 5.96 (m, 1H), 5.83 (m, 1H), 5.15-5.00 (m, 2H), 4.96 (s, 2H), 4.40-4.20 (br, 2H), 2.38 (s, 3H), 2.23 (s, 3H), 2.18 (s, 3H), 2.14 (s, 3H).

## Example 5(48)

4-[4,5-dimethyl-2-[N-(2-hydroxy-2-methylpropyl)-N-(5-methyl-2-furylsulfonyl)amino]phenoxy]methyl]-3-methylbenzoic acid

[0350]



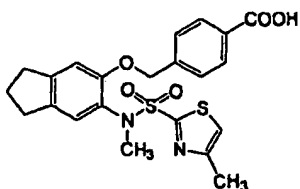
TLC : Rf 0.41 (chloroform methanol = 9 : 1);

NMR:  $\delta$  8.00-7.94 (m, 2H), 7.53 (d, J = 7.8 Hz, 1H), 6.80 (s, 1H), 6.77 (s, 1H), 6.75 (d, J = 3.3 Hz, 1H), 6.01 (m, 1H), 5.08 (d, J = 12.3 Hz, 1H), 5.00 (d, J = 12.3 Hz, 1H), 3.84 (d, J = 14.4 Hz, 1H), 3.56 (d, J = 14.4 Hz, 1H), 2.42 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 2.14 (s, 3H), 1.25 (s, 3H), 1.18 (s, 3H).

## Example 5(49)

4-[6-[N-methyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]benzoic acid

[0351]



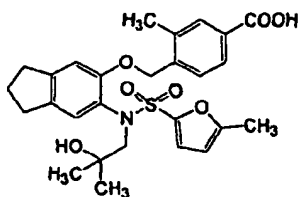
TLC : Rf 0.34 (dichloromethane : methanol = 19 : 1);

NMR :  $\delta$  8.11 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 7.20 (s, 1H), 6.94 (brs, 1H), 6.78 (s, 1H), 4.92 (brs, 2H), 3.44 (s, 3H), 2.89-2.83 (m, 4H), 2.35 (d, J = 0.9 Hz, 3H), 2.08 (m, 2H).

## Example 5(50)

4-[6-[N-(2-hydroxy-2-methylpropyl)-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxymethyl]-3-methylbenzoic acid

[0352]



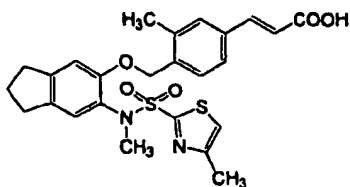
TLC : Rf 0.32 (chloroform : methanol = 10 : 1);

NMR :  $\delta$  7.97 (d, J = 7.8 Hz, 1H), 7.95 (s, 1H), 7.53 (d, J = 7.8 Hz, 1H), 6.89 (s, 1H), 6.86 (s, 1H), 6.75 (d, J = 3.3 Hz, 1H), 6.01 (dd, J = 3.3, 0.9 Hz, 1H), 5.08 (d, J = 12.9 Hz, 1H), 5.02 (d, J = 12.9 Hz, 1H), 3.85 (d, J = 14.7 Hz, 1H), 3.58 (d, J = 14.7 Hz, 1H), 2.90-2.78 (m, 4H), 2.42 (s, 3H), 2.21 (s, 3H), 2.13-2.01 (m, 2H), 1.25 (s, 3H), 1.18 (s, 3H).

## Example 5(51)

3-methyl-4-[6-[N-methyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl] cinnamic acid

[0353]



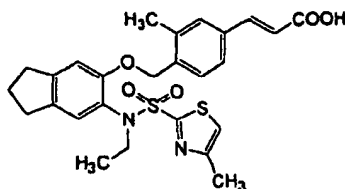
TLC : Rf 0.45 (chloroform : methanol = 9 : 1);

NMR(DMSO- $d_6$ ) :  $\delta$  7.60-7.50 (m, 3H), 7.49 (d, J = 8.1 Hz, 1H), 7.20 (d, J = 8.1 Hz, 1H), 7.09 (s, 1H), 7.04 (s, 1H), 6.53 (d, J = 15.9 Hz, 1H), 4.87 (br, 2H), 3.24 (s, 3H), 2.85 (t, J = 7.4 Hz, 2H), 2.77 (t, J = 7.4 Hz, 2H), 2.25 (s, 3H), 2.23 (s, 3H), 2.10-1.95 (m, 2H).

## Example 5(52)

4-[6-[N-ethyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]-3-methylcinnamic acid

[0354]



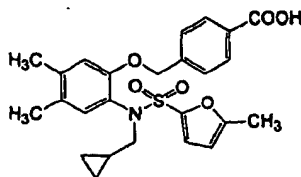
TLC Rf 0.44 (chloroform : methanol = 9 : 1);

NMR(DMSO- $d_6$ ):  $\delta$  7.55 (d, J = 16.0 Hz, 1H), 7.50-7.40 (m, 3H), 7.19 (d, J = 8.1 Hz, 1H), 7.09 (s, 1H), 6.98 (s, 1H), 6.52 (d, J = 16.0 Hz, 1H), 4.84 (br, 2H), 3.66 (br, 2H), 2.85 (t, J = 7.4 Hz, 2H), 2.77 (t, J = 7.4 Hz, 2H), 2.23 (s, 3H), 2.19 (s, 3H), 2.10-1.90 (m, 2H), 1.01 (t, J = 7.0 Hz, 3H).

## Example 5(53)

4-[2-[N-cyclopropylmethyl-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy methyl]benzoic acid

[0355]



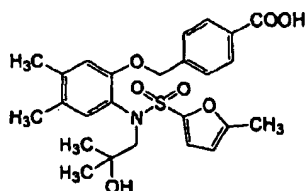
TLC: Rf 0.41 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  8.11 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.09 (s, 1H), 6.74 (d, J = 3.0 Hz, 1H), 6.70 (s, 1H), 5.96-5.92 (m, 1H), 5.02 (brs, 2H), 3.68-3.40 (m, 2H), 2.23 (s, 3H), 2.19 (s, 3H), 2.14 (s, 3H), 1.03-0.86 (m, 1H), 0.46-0.35 (m, 2H), 0.21-0.06 (m, 2H).

## Example 5(54)

4-[4,5-dimethyl-2-[N-(2-hydroxy-2-methylpropyl)-N-(5-methyl-2-furylsulfonyl)amino] phenoxy methyl]benzoic acid

[0356]



TLC Rf 0.34 chloroform : methanol = 9 : 1);

NMR :  $\delta$  8.13 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 6.81 (s, 1H), 6.75 (s, 1H), 6.74 (d, J = 3.0 Hz, 1H), 6.03-5.98 (m, 1H), 5.22-4.96 (m, 2H), 3.92-3.76 and 3.64-3.48 (each m, total 2H), 2.21 (s, 6H), 2.13 (s, 3H), 1.28 and 1.19 (each

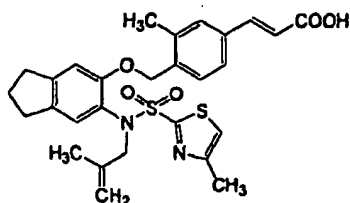


brs, each 3H).

Example 5(55)

3-methyl-4-[6-[N-(2-methyl-2-propenyl)-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]cinnamic acid

[0357]



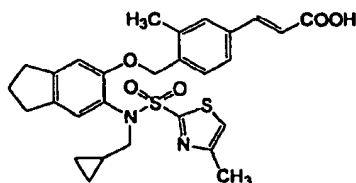
TLC : Rf 0.60 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.76 (d, J = 15.9 Hz, 1H), 7.42-7.34 (m, 2H), 7.27-7.22 (m, 1H), 7.12 (s, 1H), 6.92 (d, J = 0.9 Hz, 1H), 6.78 (s, 1H), 6.47 (d, J = 15.9 Hz, 1H), 4.90-4.72 (m, 4H), 4.50-4.14 (m, 2H), 2.92-2.80 (m, 4H), 2.31 (s, 6H), 2.18-2.00 (m, 2H), 1.81 (s, 3H).

Example 5(56)

4-[6-[N-cyclopropylmethyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]-3-methylcinnamic acid

[0358]



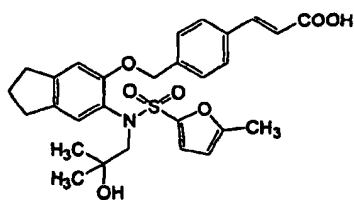
TLC: Rf 0.60 (chloroform : methanol = 9 : 1);

NMR:  $\delta$  7.77 (d, J = 15.9 Hz, 1H), 7.42-7.38 (m, 2H), 7.30-7.25 (m, 1H), 7.21 (s, 1H), 6.89 (d, J = 0.9 Hz, 1H), 6.82 (s, 1H), 6.46 (d, J = 15.9 Hz, 1H), 4.92-4.64 (m, 2H), 3.84-3.42 (m, 2H), 2.95-2.76 (m, 4H), 2.31 (s, 3H), 2.31 (s, 3H), 2.18-2.02 (m, 2H), 1.08-0.90 (m, 1H), 0.46-0.40 (m, 2H), 0.26-0.08 (m, 2H).

Example 5(57)

4-[6-[N-(2-hydroxy-2-methylpropyl)-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxymethyl]cinnamic acid

[0359]



TLC : Rf 0.46 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.78 (d, J = 15.9 Hz, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 6.85 (d, J = 3.6 Hz, 2H), 6.74 (d,

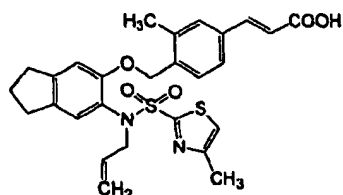
# EP 1 369 129 A1

J = 3.6 Hz, 1H), 6.47 (d, J = 15.9 Hz, 1H), 6.01 (d, J = 2.1 Hz, 1H), 5.10 (d, J = 12.0 Hz, 1H), 4.99 (d, J = 12.0 Hz, 1H), 3.85 (d, J = 14.1 Hz, 1H), 3.53 (d, J = 14.1 Hz, 1H), 2.90-2.77 (m, 4H), 2.23 (s, 3H), 2.07 (m, 2H), 1.27 (s, 3H), 1.16 (s, 3H).

## 5 Example 5(58)

3-methyl-4-[6-[N-(4-methyl-2-thiazolylsulfonyl)-N-(2-propenyl)amino]indan-5-yloxymethyl]cinnamic acid

[0360]



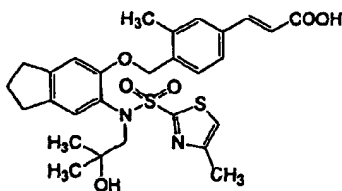
TLC : R<sub>f</sub> 0.42 (dichloromethane : methanol = 10:1);

NMR :  $\delta$  7.76 (d, J = 15.9 Hz, 1H), 7.42-7.36 (m, 2H), 7.28 (m, 1H), 7.11 (s, 1H), 6.92 (m, 1H), 6.80 (s, 1H), 6.47 (d, J = 15.9 Hz, 1H), 5.87 (m, 1H), 5.11 (dd, J = 17.1, 1.5 Hz, 1H), 5.07 (dd, J = 8.7, 1.5 Hz, 1H), 4.83 (br, 2H), 4.32 (br, 2H), 2.92-2.82 (m, 4H), 2.33 (d, J = 0.6 Hz, 3H), 2.32 (s, 3H), 2.16-2.04 (m, 2H).

## 25 Example 5(59)

4-[6-[N-(2-hydroxy-2-methylpropyl)-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]-3-methylcinnamic acid

[0361]



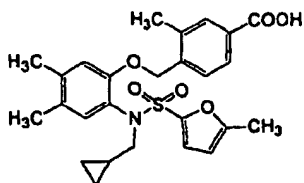
TLC : R<sub>f</sub> 0.42 (dichloromethane : methanol = 10: 1);

NMR :  $\delta$  7.76 (d, J = 15.9 Hz, 1H), 7.44-7.38 (m, 3H), 7.05 (m, 1H), 6.88 (s, 1H), 6.82 (s, 1H), 6.46 (d, J = 15.9 Hz, 1H), 5.03 (d, J = 12.0 Hz, 1H), 4.93 (d, J = 12.0 Hz, 1H), 3.96 (d, J = 14.4 Hz, 1H), 3.69 (d, J = 14.4 Hz, 1H), 2.87 (t, J = 7.5 Hz, 2H), 2.77 (t, J = 7.5 Hz, 2H), 2.43 (s, 3H), 2.40 (s, 3H), 2.13-2.00 (m, 2H), 1.23 (s, 3H), 1.18 (s, 3H).

## 45 Example 5(60)

4-[4,5-dimethyl-2-[N-cyclopropylmethyl-N-(5-methyl-2-furylsulfonyl)amino]phenoxy]methyl]-3-methylbenzoic acid

[0362]



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TLC : Rf 0.45 (chloroform : methanol = 9 : 1);

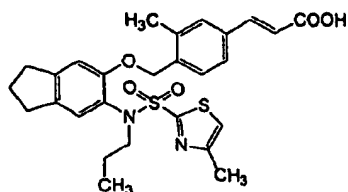
NMR :  $\delta$  8.00-7.92 (m, 2H), 7.47 (d, J = 7.8 Hz, 1H), 7.09 (s, 1H), 6.78-6.71 (m, 2H), 5.94 (m, 1H), 4.96 (s, 2H), 3.63-3.45 (br, 2H), 2.37 (s, 3H), 2.25 (s, 3H), 2.19 (s, 3H), 2.13 (s, 3H), 0.95 (m, 1H), 0.44-0.35 (m, 2H), 0.15-0.22 (m, 2H).

## 5 Example 5(61)

3-methyl-4-[6-[N-(4-methyl-2-thiazolylsulfonyl)-N-propylamino]indan-5-yloxymethyl] cinnamic acid

[0363]

10



15

20 TLC : Rf 0.41 (chloroform : methanol = 9 : 1);

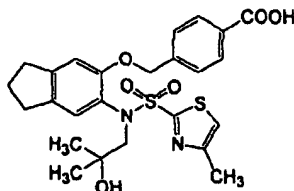
NMR :  $\delta$  7.76 (d, J = 16.2 Hz, 1H), 7.44-7.34 (m, 2H), 7.32-7.20 (m, 1H), 7.13 (s, 1H), 6.90 (s, 1H), 6.82 (s, 1H), 6.46 (d, J = 16.2 Hz, 1H), 4.90-4.70 (m, 2H), 3.90-3.50 (m, 2H), 2.89 (t, J = 7.5 Hz) and 2.86 (t, J = 7.5 Hz) total 4H, 2.31 (s) and 2.30 (s) total 6H, 2.09 (quint, J = 7.5 Hz, 2H), 1.58 (m, 2H), 0.91 (t, J = 7.5 Hz, 3H).

## 25 Example 5(62)

4-[6-[N-(2-hydroxy-2-methylpropyl)-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]benzoic acid

[0364]

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35

40 TLC : Rf 0.29 (dichloromethane : methanol = 19 : 1);

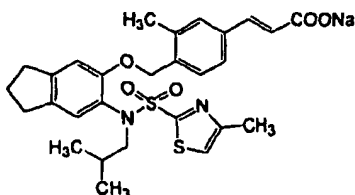
NMR :  $\delta$  8.13 (d, J = 7.8 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 7.02 (brs, 1H), 6.90 (s, 1H), 6.83 (s, 1H), 5.12 (d, J = 12.6 Hz, 1H), 4.95 (d, J = 12.6 Hz, 1H), 3.96 (d, J = 15.0 Hz, 1H), 3.77 (d, J = 15.0 Hz, 1H), 2.88-2.75 (m, 4H), 2.42 (s, 3H), 2.06 (m, 2H), 1.29 (s, 3H), 1.22 (s, 3H).

## 45 Example 6

3-methyl-4-[6-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl] cinnamic acid sodium salt

[0365]

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[0366] To a suspension of the compound prepared in example 2(74) (213 g) in ethanol (2 L), 5N aqueous solution of sodium hydroxide (74.7 ml) was added. The mixture was stirred for 0.5 hour at 80 °C. The reaction solution was filtered under heating to remove the insolubles, then the mixture was cooled, and the precipitate was collected. The mother liquor was concentrated and the residue was dissolved in ethanol (500 ml) and water (25 ml) under heating. The mixture was filtered under heating to remove the insolubles, then the mixture was cooled, and the precipitate was collected. Under heating, all collected solids were dried under reduced pressure to give the compound of the present invention (165 g) having the following physical data.

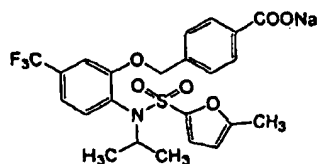
TLC : Rf 0.52 (chloroform : methanol = 9 : 1);

NMR(DMSO- $d_6$ ) :  $\delta$  7.49 (s, 1H), 7.29 (s, 1H), 7.26 (d, J = 8.1 Hz, 1H), 7.10-7.00 (m, 4H), 6.38 (d, J = 15.9 Hz, 1H), 4.89 (br-d, J = 10.5 Hz, 1H), 4.63 (br-d, J = 10.5 Hz, 1H), 3.55-3.25 (m, 2H), 2.85 (t, J = 7.2 Hz, 2H), 2.78 (t, J = 7.2 Hz, 2H), 2.21 (s, 3H), 2.18 (s, 3H), 2.10-1.90 (m, 2H), 1.60-1.45 (m, 1H), 1.00-0.70 (m, 6H).

Example 6(1)

4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-5-trifluoromethylphenoxy]benzoic acid sodium salt

[0367]



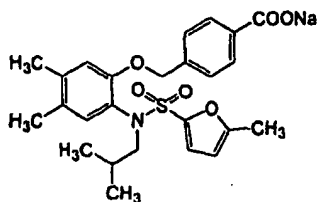
TLC : Rf 0.50 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.84 (d, J = 8.1 Hz, 2H), 7.20-6.95 (m, 5H), 6.65 (d, J = 3.3 Hz, 1H), 5.84 (d, J = 3.3 Hz, 1H), 4.75 (brs, 2H), 4.30-4.10 (m, 1H), 2.12 (s, 3H), 0.86 (brd, J = 3.9 Hz, 6H).

Example 6(2)

4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy]benzoic acid sodium salt

[0368]



TLC : Rf 0.40 (chloroform : methanol = 9 : 1);

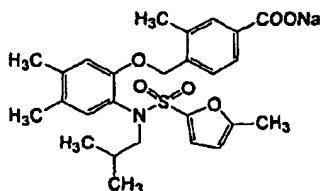
NMR :  $\delta$  7.83 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 8.1 Hz, 2H), 6.88 (s, 1H), 6.59 (s, 1H), 6.54 (d, J = 3.0 Hz, 1H), 5.74 (s, 1H), 4.90-4.50 (m, 2H), 3.33 (brd, J = 6.3 Hz, 2H), 2.09 (s, 3), 2.05 (s, 3H), 1.93 (s, 3H), 1.60-1.40 (m, 1H), 0.73 (d, J = 6.3 Hz, 6H).

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## Example 6(3)

3-methyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4,5-dimethylphenoxy methyl]benzoic acid sodium salt.

[0369]



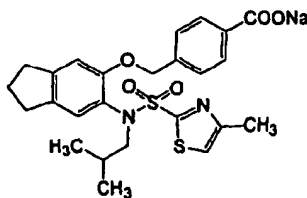
TLC : Rf 0.41 (chloroform : methanol = 9 : 1);

NMR(DMSO-d<sub>6</sub>) : δ 7.70 (s, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 6.99 (s, 1H), 6.91 (s, 1H), 6.76 (d, J = 3.3 Hz, 1H), 6.14 (d, J = 3.3 Hz, 1H), 4.88 (brs, 2H), 3.36 (d, J = 6.9 Hz, 2H), 2.26 (s, 3H), 2.22 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 1.60-1.45 (m, 1H), 0.81 (brd, J = 6.3 Hz, 6H).

## Example 6(4)

4-[6-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]benzoic acid sodium salt

[0370]



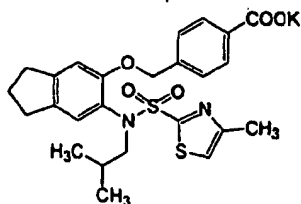
TLC: Rf 0.40 (chloroform: methanol = 9 : 1);

NMR(CD<sub>3</sub>OD) : δ 7.91 (d, J = 8.1 Hz, 2H), 7.19 (s, 1H), 7.18 (d, J = 8.1 Hz, 2H), 7.13 (s, 1H), 6.93 (s, 1H), 5.00-4.80 (m, 1H), 4.65-4.58 (m, 1H), 3.65-3.48 (m, 2H), 2.95-2.80 (m, 4H), 2.21 (d, J = 0.9 Hz, 3H), 2.09 (quint, J = 7.5 Hz, 2H), 1.66 (m, 1H), 1.03-0.85 (m, 6H).

## Example 6(5)

4-[6-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]benzoic acid potassium salt

[0371]



TLC : Rf 0.37 (chloroform : methanol = 9 : 1);

NMR(DMSO-d<sub>6</sub>) : δ 7.81 (d, J = 8.0 Hz, 2H), 7.47 (q, J = 0.4 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.03 (s, 2H), 6.95 (s, 1H), 5.10-4.80 (m, 1H), 4.80-4.50 (m, 1H), 3.43 (brs, 2H), 2.80 (q, J = 7.0 Hz, 4H), 2.23 (d, J = 0.4 Hz, 3H), 2.01 (qn,

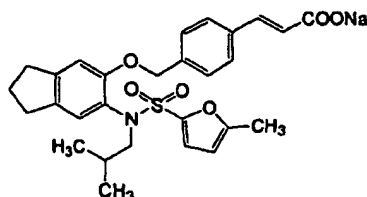
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J = 7.0 Hz, 2H), 1.53 (sept, J = 6.6 Hz, 1H), 0.85 (brs, 6H).

Example 6(6)

4-[6-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxymethyl]cinnamic acid sodium salt

[0372]



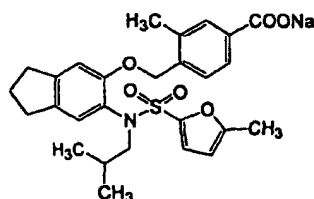
TLC : Rf 0.51 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.37 (d, J = 15.9 Hz, 1H), 7.17 (d, J = 7.5 Hz, 2H), 7.10-6.90 (m, 3H), 6.67 (s, 1H), 6.55 (s, 1H), 6.45 (d, J = 15.9 Hz, 1H), 5.74 (s, 1H), 4.80-4.45 (m, 2H), 3.35 (d, J = 6.3 Hz, 2H), 2.85-2.55 (m, 4H), 2.10-1.80 (m, 5H), 1.65-1.40 (m, 1H), 0.74 (brs, 6H).

Example 6(7)

3-methyl-4-[6-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxymethyl] benzoic acid sodium salt

[0373]



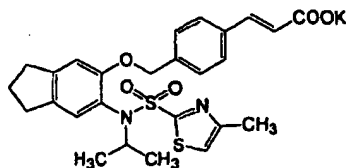
TLC : Rf 0.60 (chloroform : methanol = 9 : 1);

NMR(CD<sub>3</sub>OD) :  $\delta$  7.78 (s) and 7.75 (d, J = 8.1 Hz) total 2H, 7.24 (d, J = 8.1 Hz, 1H), 7.07 (s, 1H), 6.97 (s, 1H), 6.64 (d, J = 3.3 Hz, 1H), 6.03 (dd, J = 3.3, 0.9 Hz, 1H), 5.08-4.75 (m, 2H), 3.48 (d, J = 7.5 Hz, 2H), 2.94-2.80 (m, 4H), 2.32 (s, 3H), 2.15-2.00 (m) and 2.04 (s) total 5H, 1.87 (m, 1H), 0.98-0.80 (m, 6H).

Example 6(8)

4-[6-[N-isopropyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxymethyl]cinnamic acid potassium salt

[0374]



TLC : Rf 0.36 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.27 (d, J = 15.9 Hz, 1H), 7.21 (d, J = 7.5 Hz, 2H), 6.98 (d, J = 7.5 Hz, 2H), 6.84 (s, 1H), 6.78 (s, 1H), 6.70

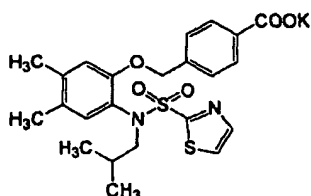
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(s, 1H), 6.41 (d, J = 15.9 Hz, 1H), 4.70-4.40 (m, 3H), 2.85-2.60 (m, 4H), 2.24 (s, 3H), 2.05-1.90 (m, 2H), 1.01 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H).

Example 6(9)

4-[2-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxyethyl]benzoic acid potassium salt

[0375]



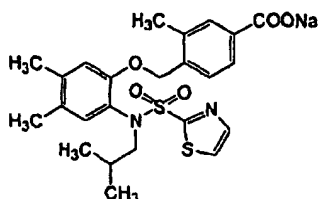
TLC : Rf 0.32 (chloroform : methanol = 9 : 1);

NMR :  $\delta$  7.82 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 3.0 Hz, 1H), 7.15 (d, J = 3.0 Hz, 1H), 6.94 (s, 1H), 6.89 (d, J = 8.1 Hz, 2H), 6.56 (s, 1H), 4.70-4.55 (m, 1H), 4.45-4.25 (m, 1H), 3.60-3.30 (m, 2H), 2.09 (s, 6H), 1.60-1.45 (m, 1H), 0.78 (brs, 3H), 0.72 (brs, 3H).

Example 6(10)

3-methyl-4-[2-[N-isobutyl-N-(2-thiazolylsulfonyl)amino]-4,5-dimethylphenoxyethyl] benzoic acid sodium salt

[0376]



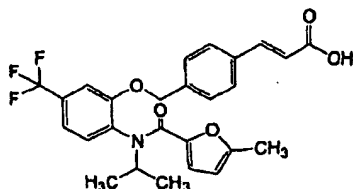
TLC : Rf 0.37 (chloroform : methanol = 10 : 1);

NMR(DMSO- $d_6$ ) :  $\delta$  7.98 (d, J = 3.0 Hz, 1H), 7.82 (d, J = 3.0 Hz, 1H), 7.64 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H), 6.97 (s, 1H), 6.91 (s, 1H), 5.00-4.54 (m, 2H), 3.42 (d, J = 6.3 Hz, 2H), 2.20 (s, 3H), 2.20 (s, 3H), 2.11 (s, 3H), 1.50 (m, 1H), 0.90-0.73 (m, 6H).

## Example 7

4-[5-trifluoromethyl-2-[N-(5-methyl-2-furylcarbonyl)-N-isopropylaminophenoxymethyl] cinnamic acid

[0377]



[0378] By the same procedures as described in specification of WO 98/27053 as Example 59(2) using the corresponding compound, the title compound having the following physical data was obtained.

TLC : R<sub>f</sub> 0.38 (chloroform : methanol = 10 : 1);

NMR :  $\delta$  7.75 (d, J = 15.9 Hz, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.37-7.16 (m, 5H), 6.45 (d, J = 15.9 Hz, 1H), 5.98 (m, 1H), 5.81 (d, J = 3.3 Hz, 1H), 5.12-4.90 (m, 3H), 2.05 (s, 3H), 1.33-0.396 (m, 6H).

Formulation example 1: preparation of capsules

[0379] The following components were admixed and granulated in conventional method, and then they were filled in second hard capsules to obtain 100 capsules each containing 100 mg of active ingredient.

- The compound A ..... 10.0 g
- Lactose ..... 6.09 g
- Microcrystalline cellulose ..... 2.61 g
- Low-substituted hydroxypropylcellulose ..... 2.0 g
- Hydroxypropylcellulose ..... 1.0 g
- light silicic anhydride ..... 0.1 g
- Magnesium stearate ..... 0.2 g

Formulation example 2: preparation of tablets

[0380] The following components were admixed, granulated and punched out in conventional method and then they were coated to obtain film-coated 100 tablets each containing 100 mg of active ingredient.

- The compound B ..... 10.0 g
- Lactose ..... 5.88 g
- Corn Starch ..... 2.52 g
- Low-substituted hydroxypropylcellulose ..... 1.00 g
- Hydroxypropylcellulose ..... 0.60 g
- Magnesium stearate ..... 0.20 g

Coating Composition

[0381]

- Hydroxypropylmethylcellulose ..... 0.3 g
- Polyethyleneglycole ..... 0.03 g
- Titanium oxide ..... 0.10 g

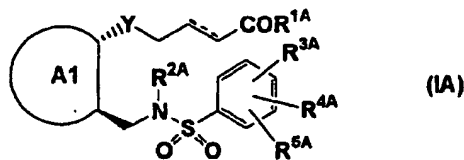
## Claims

1. A pharmaceutical composition for the treatment and/or prevention of depression, which comprises the EP<sub>1</sub> antag-



onist as active ingredient.

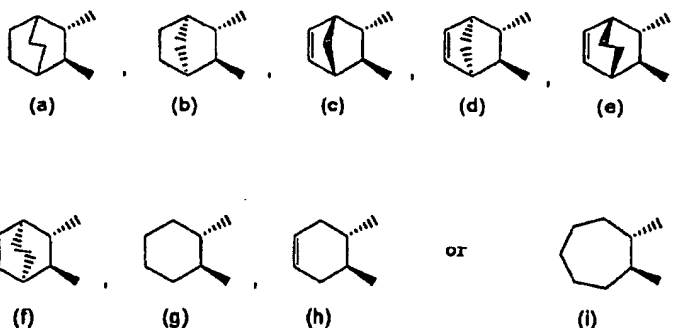
2. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 1, wherein EP<sub>1</sub> antagonist is benzenesulfonamide derivative of formula (IA)



wherein



is



R<sup>1A</sup> is hydroxy, C1-4 alkoxy or a group of formula  
NR<sup>6A</sup>R<sup>7A</sup>

in which R<sup>6A</sup> and R<sup>7A</sup> each independently, is hydrogen or C1-4 alkyl,

R<sup>2A</sup> is hydrogen or C1-4 alkyl,

R<sup>3A</sup> and R<sup>4A</sup> are C1-4 alkyl, halogen atom or trifluoromethyl,

R<sup>6A</sup> is hydrogen, C1-4 alkyl, halogen atom or trifluoromethyl,

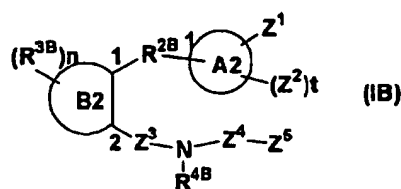
Y is cis-vinylene or trans-vinylene

is a single bond or a double bond:

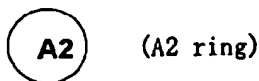
a non-toxic salt thereof or a cyclodextrin clathrate thereof.

3. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 2, wherein EP<sub>1</sub> antagonist is 6-[(2S, 3S)-3-(4-chloro-2-methylphenylsulfonylaminomethyl)-bicyclo[2.2.2]octan-2-yl]-5Z-hexenoic acid, or a non-toxic salt thereof, an acid addition salt thereof or a cyclodextrin clathrate thereof.

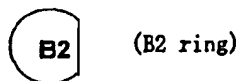
4. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 1, wherein EP<sub>1</sub> antagonist is benzenesulfonamide or carbamide derivative of formula (IB)



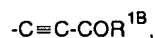
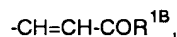
wherein



and



each independently, is C5-15 carbocyclic ring or 5-7 membered heterocyclic ring containing 1 or 2 of oxygens, sulfurs or nitrogens,  
 $Z^1$  is



in which  $R^{1B}$  is hydroxy, C1-4 alkoxy or  $\text{NR}^{6B}\text{R}^{7B}$  in which  $R^{6B}$  and  $R^{7B}$  each independently, is hydrogen or C1-4 alkyl; or



$Z^2$  is hydrogen, C1-4 alkyl, C1-4 alkoxy, nitro, halogen atom, trifluoromethyl, trifluoromethoxy, hydroxy or  $\text{COR}^{1B}$  in which  $R^{1B}$  as hereinafter defined;

$Z^3$  is a single bond or C1-4 alkylene,

$Z^4$  is  $\text{SO}_2$  or CO,

$Z^5$  is (1) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl, (2) phenyl, C3-7 cycloalkyl or 5-7 membered heterocyclic ring containing 1-2 of oxygens, sulfurs or nitrogens, (3) C1-4 alkyl, C2-4 alkenyl or C2-4 alkynyl substituted by phenyl or C3-7 cycloalkyl,

in the above (2) and (3), phenyl, C3-7 cycloalkyl and 5-7 membered heterocyclic ring containing 1-2 of oxygens, sulfurs or nitrogens may be substituted by 1-5 of  $R^{5B}$  in which multiple  $R^{5B}$  each independently, is hydrogen, C1-6 alkyl, C1-6 alkoxy, C1-6 alkylthio, nitro, halogen atom, trifluoromethyl, trifluoromethoxy or hydroxy;

$R^{2B}$  is  $\text{CONR}^{8B}$ ,  $\text{NR}^{8B}\text{CO}$ ,  $\text{CONR}^{8B}\text{-C1-4 alkylene}$ , C1-4 alkylene- $\text{CONR}^{8B}$ ,  $\text{NR}^{8B}\text{CO-C1-4 alkylene}$ , C1-4 alkylene- $\text{NR}^{8B}\text{CO}$ , C1-3 alkylene- $\text{CONR}^{8B}\text{-C1-3 alkylene}$ , C1-3 alkylene- $\text{NR}^{8B}\text{CO-C1-3 alkylene}$ , in which  $R^{8B}$  is hydrogen or C1-4 alkyl; oxygen, sulfur,  $\text{NZ}^6$  in which  $Z^6$  is hydrogen or C1-4 alkyl;  $-\text{Z}^7\text{-C1-4 alkylene}$ , C1-4 alkylene- $\text{Z}^7$ , C1-3 alkylene- $\text{Z}^7\text{-C1-3 alkylene}$  in which  $Z^7$  is oxygen, sulfur or  $\text{NZ}^6$  in which  $Z^6$  is as hereinbefore defined; CO, CO-C1-4 alkylene, C1-4 alkylene-CO, C1-3 alkylene-CO-C1-3 alkylene, C2-4 alkylene, C2-4 alkenylene, C2-4 alkynylene,

$R^{3B}$  is hydrogen, C1-6 alkyl, C1-6 alkoxy, C1-6 alkylthio, nitro, halogen atom, trifluoromethyl, trifluoromethoxy, hydroxy or hydroxymethyl,

$R^{4B}$  is (1) hydrogen, (2) C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl, (3) C1-6 alkyl substituted by 1-2 of  $COOZ^B$ ,  $CONZ^9Z^{10}$ ,  $OZ^B$  in which  $Z^B$ ,  $Z^9$  and  $Z^{10}$  each independently, is hydrogen or C1-4 alkyl; and C1-4 alkoxy-C alkoxy, (4) C3-7 cycloalkyl, (5) C1-4 alkyl, C2-4 alkenyl or C2-4 alkynyl substituted by phenyl or C3-7 cycloalkyl, in the above (4) and (5), phenyl, C3-7 cycloalkyl may be substituted by 1-5 of  $R^{5B}$  in which  $R^{5B}$  is as hereinbefore defined,

n and t each independently, is 1-4,

with the proviso that (1)  $R^{2B}$  bond to atom of only 1-position in  $B^2$  ring and  $R^{3B}$  bond to atom of only 2-position in  $B^2$  ring,

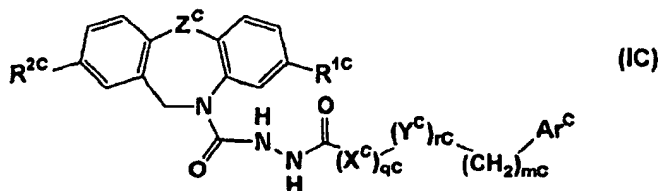
(2) when  $A^2$  ring is benzene and  $(Z^2)_t$  is not  $COR^{1B}$ , then  $Z^1$  bond only 3 or 4-position in benzene of  $A^2$  ring; or a non-toxic salt thereof.

5. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 4, wherein  $EP_1$  antagonist is

(1) 4-[2-(N-isobutyl-2-furanylsulfonylamino)-5-trifluoromethylphenoxyethyl] cinnamic acid,

(2) 4-[5-trifluoromethyl-2-[N-(5-methyl-2-furylcarbonyl)-N-isopropylamino] phenoxyethyl]cinnamic acid, or a non-toxic salt thereof.

6. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 1, wherein  $EP_1$  antagonist is a compound of formula (IC)



wherein  $R^{1C}$  is hydrogen, halogen atom or  $-CF_3$ ,

$R^{2C}$  is hydrogen, halogen atom,  $-OH$  or  $-OCH_3$ ,

$Z^C$  is oxygen, sulfur,  $-S(O)-$  or  $-S(O)_2-$ ,

$X^C$  is  $-CH=CH-$ ,  $-CF_2-$ ,  $-CHF-$ ,  $-(CH_2)_{nc}-$  or  $-(CH_2)_{pc}-CH=CH-$ ,

$Y^C$  is  $-CH(OH)-$ ,  $-NR^{3C}-$ , sulfur,  $-S(O)-$ ,  $-S(O)_2-$  or oxygen,

$q^C$  is 0 or 1,

$r^C$  is 0 or 1, with the proviso that in the case of following (1), (2) or (3),  $r^C$  is not 0:

(1)  $X^C$  is  $-CH=CH-$ ,  $-(CH_2)_{nc}-$  or  $-(CH_2)_{pc}-CH=CH-$ ,  $q^C$  is 1 and  $Ar^C$  is imidazole or phenyl,

(2)  $X^C$  is  $-(CH_2)_{nc}-$ ,  $q^C$  is 1,  $n^C$  is 1 and  $Ar^C$  is ethylphenyl substituted by halogen atom, methyl or alkoxy,

(3)  $q^C$  is 1,  $m^C$  is 1, 2, 3, 4, 5 or 6 and  $Ar^C$  is imidazole or phenyl,

$m^C$  is 0-6, with the proviso that when  $X^C$  is  $-(CH_2)_{nc}-$ ,  $q^C$  is 1,  $Y^C$  is oxygen, sulfur,  $-S(O)-$  or  $-S(O)_2-$  and  $Ar^C$  is phenyl, and then  $m^C$  is not 0,

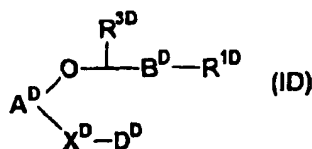
$n^C$  is 1-6,

$p^C$  is 1-6,

$R^{3C}$  is hydrogen or t-butyloxycarbonyl,

$Ar^C$  is aryl, alkyl-substituted aryl or aryl-substituted aryl.

7. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 1, wherein  $EP_1$  antagonist is a compound of formula (ID)



wherein  $A^D$  is an optionally substituted: 8-10 membered bicyclic heteroaryl, 5-6 membered heteroaryl, naphthyl or phenyl, with the proviso that  $-OCH(R^{3D})-$  and  $-X^D$ -linking group are positioned in a 1, 2 relationship to one another on ring carbon atoms,

$B^D$  is an optionally substituted 5-6 membered heteroaryl ring system or optionally substituted phenyl,

$D^D$  is optionally substituted: pyridyl, pyrazinyl, pyrimidyl, pyridazyl, pyrrolyl, thienyl, furyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl or phenyl,

$X^D$  is  $-(CHR^{4D})_{nD}-$  or  $-CHR^{4D})_{pD}CR^{4D}=CR^{4D}(CHR^{4D})_{qD}-$ , in which  $n^D$  is 1-3, and  $p^D$  and  $q^D$  are either both 0 or one of  $p^D$  and  $q^D$  is 1 and the other is 0,

$R^{1D}$  is positioned on ring  $B^D$  in a 1, 3 or 1,4 relationship with the  $-OCH(R^{3D})-$  linking group in 6-membered rings and in a 1, 3 relationship with  $-OCH(R^{3D})-$  linking group in 5-membered rings and carboxy, carboxy-C1-3 alkyl, tetrazolyl, tetrazolyl-C1-3 alkyl, tetrionic acid, hydroxamic acid or sulphonic acid, or

$R^{1D}$  is  $-CONR^{aD}R^{a1D}$  in which  $R^{aD}$  is hydrogen or C1-6 alkyl,  $R^{a1D}$  is hydrogen, or optionally substituted C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-7 cycloalkyl, C3-7 cycloalkyl-C1-6 alkyl, C3-7 cycloalkyl-C2-6 alkenyl, C3-7 cycloalkyl-C2-6 alkynyl, C5-7 cycloalkenyl, C3-7 cycloalkenyl-C1-6 alkyl, C5-7 cycloalkenyl-C2-6 alkenyl, C5-7 cycloalkenyl-C2-6 alkynyl, C1-3 alkyl substituted by 5-6 membered saturated or partially saturated heterocyclic ring, 5-6 membered saturated or partially saturated heterocyclic ring or 5-6 membered heteroaryl, or  $R^{aD}$  and  $R^{a1D}$  together with the amide nitrogen to which they are attached ( $NR^{aD}R^{a1D}$ ) form an amino acid residue or ester thereof, or

$R^{1D}$  is  $-CONHSO_2R^{bD}$  in which  $R^{bD}$  is optionally substituted C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-7 cycloalkyl-C1-6 alkyl, C3-7 cycloalkyl-C2-6 alkenyl, C3-7 cycloalkyl-C2-6 alkynyl, C3-7 cycloalkenyl-C1-6 alkyl, C3-7 cycloalkenyl-C2-6 alkenyl, C3-7 cycloalkenyl-C2-6 alkynyl, 5-6 membered heteroaryl, 5-6 membered heteroaryl-C1-6 alkyl, phenyl, phenyl-C1-6 alkyl, 5-6 membered saturated or partially saturated heterocyclic ring or 5-6 membered saturated or partially saturated heterocyclic ring-C1-6 alkyl,

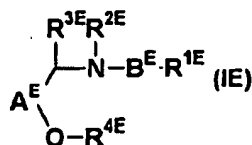
$R^{3D}$  is hydrogen or C1-4 alkyl,

$R^{4D}$  is hydrogen or C1-4 alkyl,

with the proviso that 4-(2-benzyl-3-hydroxy-4-formylphenoxy)methyl-3-methoxybenzoic acid and 4-(2-(3-phenylprop-2-ene-1-yl)-3-hydroxy-4-formylphenoxy)methyl-3-methoxybenzoic acid are excluded;

or N-oxide thereof, or S-oxide of sulfur containing rings, or a pharmaceutically acceptable salt thereof or in vivo hydrolyzable ester or amide thereof.

8. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 1, wherein  $EP_1$  antagonist is a compound of formula (IE)



wherein  $A^E$  is optionally substituted: phenyl, naphthyl, pyridyl, pyrazinyl, pyridazynyl, pyrimidyl, thienyl, thiazolyl, oxazolyl or thiadiazolyl having at least two adjacent ring carbon atoms, with the proviso that  $-CH(R^{3E})N(R^{2E})B^E-R^{1E}$  and  $-OR^{4E}$  are positioned in a 1, 2 relationship to one another on ring carbon atom and the ring atom position ortho to the  $OR^{4E}$  linking group (and therefor in the 3-position relative to the  $-CH(R^{3E})N(R^{2E})B^E$ -linking group) is not substituted,

$B^E$  is optionally substituted: phenyl, pyridyl, thiazolyl, oxazolyl, thienyl, thiadiazolyl, imidazolyl, pyrazinyl, pyridazynyl or pyrimidyl,

R<sup>1E</sup> is positioned on ring B<sup>E</sup> in a 1, 3 or 1, 4 relationship with —CH(R<sup>3E</sup>)N(R<sup>2E</sup>)— linking group and is carboxy, carboxy-C1-3 alkyl, tetrazolyl, tetrazolyl-C1-3 alkyl, tetrionic acid, hydroxamic acid, sulphonic acid, or

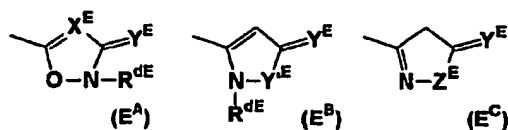
R<sup>1E</sup> is —CONR<sup>aE</sup>R<sup>a1E</sup> in which R<sup>aE</sup> is hydrogen or C1-6 alkyl, R<sup>a1E</sup> is hydrogen, C1-6 alkyl (optionally substituted by halogen atom, amino, C1-4 alkylamino, di-C1-4 alkylamino, hydroxy, nitro, cyano, trifluoromethyl, C1-4 alkoxy or C1-4 alkoxy-carbonyl), C2-6 alkenyl (the double bond is not in the 1-position), C2-6 alkynyl (the triple bond is not in the 1-position), carboxyphenyl, 5-6 membered heterocyclyl-C1-3 alkyl, 5-6 membered heteroaryl-C1-3 alkyl, 5-6 membered heterocyclyl or 5-6 membered heteroaryl, or R<sup>aE</sup> and

R<sup>a1E</sup> together with the amide nitrogen to which they are attached (NR<sup>aE</sup>R<sup>a1E</sup>) form an amino acid residue or ester thereof, or

R<sup>1E</sup> is —CONHSO<sub>2</sub>R<sup>bE</sup> in which R<sup>bE</sup> is C1-6 alkyl (optionally substituted by halogen atom, hydroxy, nitro, cyano, trifluoromethyl, C1-4 alkoxy, amino, C1-4 alkylamino, di-C1-4 alkylamino or C1-4 alkoxy-carbonyl), C2-6 alkenyl (the double bond is not in the 1-position), C2-6 alkynyl (the triple bond is not in the 1-position), 5-6 membered heterocyclyl-C1-3 alkyl, 5-6 membered heteroaryl-C1-3 alkyl, 5-6 membered heterocyclyl or 5-6 membered heteroaryl or phenyl,

wherein any heterocyclyl or heteroaryl group in R<sup>a1E</sup> is optionally substituted by halogen atom, hydroxy, nitro, amino, cyano, C1-6 alkoxy, C1-6 alkyl-S(O)<sub>pE</sub>— (p<sup>E</sup> is 0, 1 or 2), C1-6 alkylcarbamoyl, C1-4 alkylcarbamoyl, di(C1-4 alkyl)carbamoyl, C2-6 alkenyl, C2-6 alkynyl, C1-4 alkoxy-carbonylamino, C1-4 alkanoylamino, C1-4 alkanoyl (N-C1-4 alkyl)amino, C1-4 alkanesulfonamide, benzenesulfonamide, aminosulfonyl, C1-4 alkylaminosulfonyl, di(C1-4 alkyl)aminosulfonyl, C1-4 alkoxy-carbonyl, C-4 alkanoyloxy, C1-6 alkanoyl, formyl-C1-4 alkyl, hydroxyimino-C1-6 alkyl, C1-4 alkoxyimino-C1-6 alkyl or C1-6 alkylcarbamoylamino, or

R<sup>1E</sup> is —SO<sub>2</sub>N(R<sup>cE</sup>)R<sup>c1E</sup> in which R<sup>cE</sup> is hydrogen or C1-4 alkyl and R<sup>c1E</sup> is hydrogen or C1-4 alkyl, or R<sup>1E</sup> is the formula (E<sup>A</sup>), (E<sup>B</sup>) or (E<sup>C</sup>):



wherein X<sup>E</sup> is CH or nitrogen,

Y<sup>E</sup> is oxygen or sulfur,

Y<sup>E</sup> is oxygen or NR<sup>dE</sup> and

Z<sup>E</sup> is CH<sub>2</sub>, NR<sup>dE</sup> or oxygen, with the proviso that there is no more than one ring oxygen and there are at least two ring heteroatoms and wherein R<sup>dE</sup> is hydrogen or C1-4 alkyl,

R<sup>2E</sup> is hydrogen, C1-6 alkyl optionally substituted by hydroxy, cyano or trifluoromethyl,

C2-6 alkynyl (the double bond is not in the 1-position), C2-6 alkynyl (the triple bond is not in the 1-position), phenyl-C1-3 alkyl or pyridyl-C1-3 alkyl,

R<sup>3E</sup> is hydrogen, methyl or ethyl,

R<sup>4E</sup> is optionally substituted: C1-6 alkyl, C3-7 cycloalkyl-C1-3 alkyl or C3-7 cycloalkyl, with the proviso that 2-[2-methoxybenzylamino]pyridine-5-carboxylic acid, 4-[2-methoxybenzylamino]benzoic acid, 5-[2, 3-dimethoxybenzylamino]-2-chloro-3-aminosulfonylbenzoic acid and 5-[2, 5-dimethoxybenzylamino]-2-hydroxybenzoic acid are excluded;

or N-oxide of —NR<sup>2E</sup>—, or S-oxide of sulfur containing rings, or a pharmaceutically acceptable salt thereof or in vivo hydrolyzable ester or amide thereof.

9. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 1, wherein EP<sub>1</sub> antagonist is a compound of formula (IF)

$$\begin{array}{c} R^{1F}R^{2F}R^{3F}-HET^F \\ | \\ A^F \\ | \\ X^F-B^F-C(=O)-Z^F \end{array} \quad (1F)$$

wherein HET<sup>F</sup> is 5-12 membered mono- or bi-cyclic aromatic ring containing 0-3 heteroatoms selected from oxygen, S(O)<sub>nF</sub> and N(O)<sub>mF</sub>, in which m<sup>F</sup> is 0 or 1, n<sup>F</sup> is 0, 1 or 2, A<sup>F</sup> is -W<sup>F</sup>-, -C(O)-, -C(R<sup>7F</sup>)-W<sup>F</sup>-, -W<sup>F</sup>-C(R<sup>7F</sup>)<sub>2</sub>-, -CR<sup>7F</sup> (OR<sup>20F</sup>)-, -C(R<sup>7F</sup>)<sub>2</sub>-, -C(R<sup>7F</sup>)<sub>2</sub>-C(OR<sup>20F</sup>)R<sup>7F</sup>-, -C(R<sup>7F</sup>)<sub>2</sub>-C(R<sup>7F</sup>)<sub>2</sub>- or —CR<sup>7F</sup>CR<sup>7F</sup>-, in which W<sup>F</sup> is oxygen, S(O)<sub>nF</sub> or NR<sup>17F</sup>.

X<sup>F</sup> is 5-10 membered mono- or bi-cyclic aryl or heteroaryl having 1-3 heteroatoms selected from oxygen, S(O)<sub>nF</sub> and N(O)<sub>mF</sub>, and optionally substituted by R<sup>14F</sup> and R<sup>15F</sup>, and A<sup>F</sup> and B<sup>F</sup> are attached to the aryl or heteroaryl ortho relative to each other.

Y<sup>F</sup> is O, S(O)<sub>nF</sub>, NR<sup>17F</sup>, a bond or -CR<sup>18F</sup>=CR<sup>18F</sup>;

BF is  $-(C(R^{18F})_2)_{p^F}-Y^F-(C(R^{18F})_2)_{q^F}-$ , in which  $p^F$  and  $q^F$  are independently 0-3, such that when  $Y^F$  is O,  $S(O)_{n^F}$ ,  $NR^{17F}$  or  $-CR^{18F}=CR^{18F}-$ ,  $p^F+q^F$  is 0-6, and when  $Y^F$  is a bond,  $p^F+q^F$  is 1-6;

Z<sup>F</sup> is OH, NHSO<sub>2</sub>R<sup>19F</sup>;

R<sup>1F</sup>, R<sup>2F</sup> and R<sup>3F</sup> each independently, is hydrogen, halogen atom, lower alkyl, lower alkenyl, lower alkynyl, lower alkenyl-HET<sup>F</sup>(R<sup>4F</sup>)<sub>4-9</sub>, -(C(R<sup>4F</sup>)<sub>2</sub>)<sub>pF</sub>SR<sup>5F</sup>, -(C(R<sup>4F</sup>)<sub>2</sub>)<sub>pF</sub>OR<sup>6F</sup>, -(C(R<sup>4F</sup>)<sub>2</sub>)<sub>pF</sub>N(R<sup>6F</sup>)<sub>2</sub>, CN, NO<sub>2</sub>, -(C(R<sup>4F</sup>)<sub>2</sub>)<sub>pF</sub>C(R<sup>7F</sup>)<sub>3</sub>, -COOR<sup>8F</sup>, -CON(R<sup>6F</sup>)<sub>2</sub> or -(C(R<sup>4F</sup>)<sub>2</sub>)<sub>pF</sub>S(O)<sub>nF</sub>R<sup>10F</sup>,

each R<sup>4F</sup> is hydrogen, F, CF<sub>3</sub>, lower alkyl or

two R<sup>4F</sup>, taken together, is a ring of up to six atoms, optionally containing one heteroatom selected from O, S(O)<sub>nF</sub> and N(O)<sub>mF</sub>.

each R<sup>5F</sup> is independently lower alkyl, lower alkenyl, lower alkynyl, CF<sub>3</sub>, lower alkyl-HETF, lower alkenyl-HETF, -C(R<sup>18F</sup>)<sub>2</sub>-PF<sub>6</sub>Ph(R<sup>11F</sup>)<sub>0-2</sub>,

each R<sup>6F</sup> is independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, CF<sub>3</sub>, Ph, Bn or two R<sup>6F</sup> together with N to which they are attached, is a ring of up to six atoms, optionally containing an additional heteroatom selected from O, S(O)<sub>nF</sub> and N(O)<sub>mF</sub>.

each R<sup>7F</sup> is independently hydrogen, F, CF<sub>3</sub>, lower alkyl, or two R<sup>7F</sup> taken together, is 3-6 membered aromatic or aliphatic ring containing 0-2 heteroatom selected from O, S(O)<sub>nF</sub> and N(O)<sub>mF</sub>.

each  $R^{8F}$  is hydrogen or  $R^{6F}$ .

each  $R^{9F}$  is independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, Ph or Bn, each  $R^{10F}$  is independently lower alkyl, lower alkenyl, lower alkynyl,  $CF_3$ ,  $Ph(R^{11F})_{0-3}$ ,  $CH_2Ph(R^{11F})_{0-3}$  or  $N(R^{6F})_2$ .

each R<sup>11F</sup> is independently lower alkyl, SR<sup>20F</sup>, OR<sup>20F</sup>, N(R<sup>6F</sup>)<sub>2</sub>, -COOR<sup>12F</sup>, -CON(R<sup>6F</sup>)<sub>2</sub>, COR<sup>12F</sup>, CN, CF<sub>3</sub>, NO<sub>2</sub> or halogen atom.

each R<sup>12F</sup> is independently hydrogen, lower alkyl or benzyl,

each R<sup>13F</sup> is independently hydrogen, halogen atom, lower alkyl, O-lower alkenyl, S-lower alkyl, N(R<sup>6F</sup>)<sub>2</sub>, COOR<sup>12F</sup>, CN, CF<sub>3</sub> or NO<sub>2</sub>,

R<sup>14F</sup> and R<sup>15F</sup> are independently lower alkyl, halogen atom, CF<sub>3</sub>, OR<sup>16F</sup>, S(O)<sub>nF</sub>R<sup>16F</sup> or C(R<sup>16F</sup>)<sub>2</sub>OR<sup>17F</sup>.

each R<sup>16F</sup> is independently hydrogen, lower alkyl, lower alkenyl, Ph, Bn or CF<sub>3</sub>,

each R<sup>17F</sup> is independently hydrogen, lower alkyl or Bn,

each R<sup>18F</sup> is independently hydrogen, F or lower alkyl, or two R<sup>18F</sup> taken together, is 3-6 membered ring optionally containing one heteroatom selected from oxygen, S(O)<sub>nF</sub> and nitrogen,

each R<sup>19F</sup> is independently lower alkyl, lower alkenyl, lower alkynyl, CF<sub>3</sub>, HET(R<sup>aF</sup>)<sub>4-9</sub>, lower alkyl-HETC(R<sup>aF</sup>)<sub>4-9</sub>, lower alkenyl-HET(R<sup>aF</sup>)<sub>4-9</sub>,

each R<sup>20F</sup> is independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, CF<sub>3</sub> or Ph(R<sup>13F</sup>)<sub>2</sub>,

each  $R^{aF}$  is independently selected from the following group:

hydrogen, hydroxy, halogen atom, CN, NO<sub>2</sub>, amino, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkoxy, C2-6 alkenyloxy, C2-6 alkynyloxy, C1-6 alkylamino, di(C1-6 alkyl)amino, CF<sub>3</sub>, C(O)C1-6 alkyl, C(O)C2-6 alkenyl, C(O)C2-6 alkynyl, COOH, COO(C1-6)alkyl COO(C2-6)alkenyl and COO(C2-6)alkynyl, said alkyl, alkenyl, alkynyl, and alkyl portions of alkylamino and dialkylamino being optionally substituted by 1-3 of hydroxy, halogen atom, aryl, C1-6 alkoxy, C2-6 alkenyloxy, C2-6 alkynyloxy, CF<sub>3</sub>, CO(C1-6)al CO(C2-6)alkenyl, CO(C2-6)alkynyl, COOH, COO

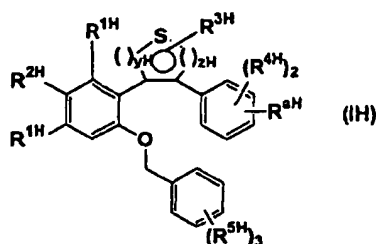
(C1-6)alkyl, COO(C2-6)alkenyl, COO(C2-6)alkynyl NH<sub>2</sub>, NH(C1-6)alkyl and N(C1-6alkyl)<sub>2</sub> ;  
or a non-toxic salt thereof.

10. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 1, wherein  
EP<sub>1</sub> antagonist is a compound of formula (IG)



wherein Ar<sup>1G</sup> is aryl or heteroaryl, optionally substituted by R<sup>1G</sup> or R<sup>3G</sup>,  
R<sup>1G</sup> is Y<sup>G</sup><sub>mG</sub>-R<sup>2G</sup>, Y<sup>G</sup><sub>mG</sub>-Ar<sup>3G</sup>, halogen atom, N(R<sup>5G</sup>)<sub>2</sub>, CN, NO<sub>2</sub>, C(R<sup>6G</sup>)<sub>3</sub>, CON(R<sup>5G</sup>)<sub>2</sub>, S(O)<sub>nG</sub>R<sup>7G</sup> or hydroxy,  
Y<sup>G</sup> is a linker between R<sup>2G</sup> or Ar<sup>3G</sup> and Ar<sup>1G</sup> containing 0-4 carbon atoms and not more than one heteroatom  
selected from oxygen, nitrogen and sulfur, said linker optionally containing CO, S(O)<sub>nG</sub>, -C=C- or acetylenic group,  
and said linker being optionally substituted by R<sup>2G</sup>,  
m<sup>G</sup> is 0 or 1,  
n<sup>G</sup> is 0, 1 or 2  
R<sup>2G</sup> is hydrogen, F, CHF<sub>2</sub>, CF<sub>3</sub>, lower alkyl or hydroxy(C1-6)alkyl, or two R<sup>2G</sup> taken together, is carbocyclic ring  
of up to six members, said ring containing not more than one heteroatom selected from oxygen, nitrogen or sulfur,  
Ar<sup>3G</sup> is aryl or heteroaryl, optionally substituted by R<sup>3G</sup>,  
R<sup>3G</sup> is R<sup>4G</sup>, halogen atom, halo(C1-6)alkyl, N(R<sup>5G</sup>)<sub>2</sub>, CN, NO<sub>2</sub>, C(R<sup>6G</sup>)<sub>3</sub>, CON(R<sup>5G</sup>)<sub>2</sub>, OR<sup>4G</sup>, SR<sup>4G</sup> or S(O)<sub>nG</sub>R<sup>7G</sup>,  
R<sup>4G</sup> is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, CHF<sub>2</sub> or CF<sub>3</sub>,  
R<sup>5G</sup> is R<sup>4G</sup>, Ph or Bn, or two R<sup>5G</sup> taken together, is a ring of up to six members containing carbon atoms and 0-2  
heteroatoms selected from oxygen, nitrogen or sulfur,  
R<sup>6G</sup> is hydrogen, F, CF<sub>3</sub> or lower alkyl, or two R<sup>6G</sup> taken together, is a ring of up to six members containing carbon  
atoms and 0-2 heteroatoms selected from oxygen, nitrogen or sulfur,  
R<sup>7G</sup> is lower alkyl, lower alkenyl, lower alkynyl, CHF<sub>2</sub>, CF<sub>3</sub>, N(R<sup>5G</sup>)<sub>2</sub>, Ph(R<sup>8G</sup>)<sub>2</sub> or CH<sub>2</sub>PhCR<sup>8G</sup>)<sub>2</sub>,  
R<sup>8G</sup> is R<sup>4G</sup>, OR<sup>4G</sup>, SR<sup>4G</sup> or halogen atom,  
W<sup>G</sup> is a 3-6 membered linking group containing 0-2 heteroatoms selected from oxygen, nitrogen and sulfur, said  
linking group optionally containing CO, S(O)<sub>nG</sub>, C=C, acetylenic group, and optionally being substituted by R<sup>9G</sup>,  
R<sup>9G</sup> is R<sup>2G</sup>, lower alkyl, lower alkynyl, OR<sup>4G</sup> or SR<sup>4G</sup>,  
Ar<sup>2G</sup> is aryl or heteroaryl, optionally substituted by R<sup>3G</sup>,  
R<sup>10G</sup> is R<sup>4G</sup>, halogen atom, N(R<sup>5G</sup>)<sub>2</sub>, CN, NO<sub>2</sub>, C(R<sup>6G</sup>)<sub>3</sub>, OR<sup>4G</sup>, SR<sup>4G</sup> or S(O)<sub>nG</sub>R<sup>7G</sup>,  
X<sup>G</sup> is a linker which is attached to Ar<sup>2G</sup> ortho to the attachment of W<sup>G</sup>, said linker containing 0-4 carbon atoms  
and not more than one heteroatom selected from oxygen, nitrogen and sulfur, said linker further optionally con-  
taining CO, S(O)<sub>nG</sub>, C=C or acetylenic group, and said linker being optionally substituted by R<sup>11G</sup>,  
R<sup>11G</sup> is R<sup>9G</sup>,  
Q<sup>G</sup> is a member selected from the group consisting of COOH, tetrazole, SO<sub>3</sub>H, hydroxamic acid, CONHSO<sub>2</sub>R<sup>12G</sup>  
and SO<sub>2</sub>NHCOR<sup>12G</sup>,  
R<sup>12G</sup> is a member selected from the group consisting of CF<sub>3</sub>, lower alkyl, lower alkenyl, lower alkynyl and Z<sup>G</sup>Ar<sup>4G</sup>,  
Z<sup>G</sup> is a linker containing 0-4 carbon atom, optionally substituted by R<sup>13G</sup>,  
R<sup>13G</sup> is R<sup>9G</sup>,  
Ar<sup>4G</sup> is aryl or heteroaryl, optionally substituted by R<sup>14G</sup>,  
R<sup>14G</sup> is R<sup>10G</sup> or NHCOMe;  
or an non-toxic salt thereof.

11. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 1, wherein  
EP<sub>1</sub> antagonist is a compound of formula (IH)



wherein  $y^H$  and  $z^H$  are independently 0-2, with the proviso that  $y^H + z^H = 2$ ,  
 $R^{6H}$  is

1) heteroaryl, wherein heteroaryl is selected from the group (a) — (n):

(a) fury, (b) diazinyl, triazinyl or tetrazinyl, (c) imidazolyl, (d) isoxazolyl, (e) isothiazolyl,  
 (f) oxadiazolyl, (g) oxazolyl, (h) pyrazolyl, (i) pyrrolyl, (j) thiadiazolyl, (k) thiazolyl, (l) thienyl, (m) triazolyl  
 and (n) tetrazolyl, wherein heteroaryl is optionally substituted by one or more substituents independently  
 selected from  $R^{11H}$  and C1-4 alkyl;

2) — $COR^{6H}$ ,

3) — $NR^{7H}R^{8H}$ ,

4) — $SO_2R^{9H}$ ,

5) hydroxy,

6) C1-6 alkoxy, optionally substituted by one or more substituents independently selected from  $R^{11H}$ , and

7) C1-6 alkyl, C2-6 alkenyl or C3-6 cycloalkyl, optionally substituted by one or more substituents independently  
 selected from  $R^{11H}$ , and further substituted by 1-3 substituents independently selected from the group of (a)  
 — (h):

(a) — $COR^{6H}$ , (b) — $NR^{7H}R^{8H}$ , (c) — $SO_2R^{9H}$ , (d) hydroxy, (e) C1-6 alkoxy or haloC1-6 alkoxy, and (f)  
 heteroaryl;

$R^{6H}$  is positioned on the phenyl ring to which it is bonded in a 1, 3 or 1, 4 relationship relative to the thienyl  
 group of formula (IH),

$R^{1H}$ ,  $R^{2H}$ ,  $R^{3H}$ ,  $R^{4H}$  and  $R^{5H}$  are independently selected from the following group:

1) hydroxy, 2) halogen atom, 3) C1-6 alkyl, 4) C1-6 alkoxy, 5) C1-6 alkylthio, 6) nitro, 7) carboxy, and 8) CN,  
 wherein groups of 3) — 5) are optionally substituted by one or more substituents independently selected from  
 $R^{11H}$ ,  $R^{6H}$  is hydrogen, hydroxy, C1-6 alkyl, C1-6 alkoxy and  $NR^{7H}R^{8H}$ , wherein C1-6 alkyl and C1-6 alkoxy  
 are optionally substituted by one or more substituents independently selected from  $R^{11H}$ ,

$R^{7H}$  and  $R^{8H}$  are independently selected from the group: 1) hydrogen, 2) hydroxy, 3)  $SO_2R^{9H}$ , 4) C1-6 alkyl,  
 5) C1-6 alkoxy, 6) phenyl, 7) naphthyl, 8) furyl, 9) thienyl and 10) pyridyl, wherein groups of 4) - 5) are optionally  
 substituted by one or more substituents independently selected from  $R^{11H}$ , and groups of 6) — 10) are op-  
 tionally substituted by one or more substituents independently selected from  $R^{11H}$  or C1-4 alkyl,

$R^{9H}$  is selected from the group:

1) hydroxy, 2)  $NCR^{10H}_2$ , 3) C1-6 alkyl, optionally substituted by one or more substituents independently se-  
 lected from  $R^{11H}$ , 4) phenyl, 5) naphthyl, 6) furyl, 7) thienyl, and 8) pyridyl, groups of 4) — 8) are optionally  
 substituted by one or more substituents independently selected from  $R^{11H}$  and C1-4 alkyl,

$R^{10H}$  is hydrogen or C1-6 alkyl,

$R^{11H}$  is halogen atom, hydroxy, C1-3 alkoxy, nitro,  $N(R^{10H})_2$ , and pyridyl;

or a pharmaceutically acceptable salt, hydrate or ester thereof.

12. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 1, wherein  
 $EP_1$  antagonist is a compound of formula (IJ)

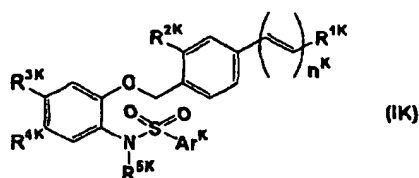


1) heteroaryl, wherein heteroaryl is selected from the group (a) — (n):

2) —COR<sup>6J</sup>,  
3) —NR<sup>7J</sup>R<sup>8J</sup>,  
4) —SO<sub>2</sub>R<sup>9J</sup>,  
5) hydroxy,  
6) C1-6 alkoxy, optionally substituted by one or more substituents independently selected from R<sup>11J</sup>, and  
7) C1-6 alkyl, C2-6 alkenyl or C3-6 cycloalkyl, optionally substituted by one or more substituents independently selected from R<sup>11H</sup>, and further substituted by 1-3 substituents independently selected from the group of (a) — (f):

1) hydroxy, 2) halogen atom, 3) C1-6 alkyl, 4) C1-6 alkoxy, 5) C1-6 alkylthio, 6) nitro, 7) carboxy, and 8) CN, wherein groups of 3) — 5) are optionally substituted by one or more substituents independently selected from R<sup>11J</sup>,  
R<sup>6J</sup> is hydrogen, hydroxy, C1-6 alkyl, C1-6 alkoxy and NR<sup>7J</sup>R<sup>8J</sup>, wherein C1-6 alkyl and C1-6 alkoxy are optionally substituted by one or more substituents independently selected from R<sup>11J</sup>, R<sup>7J</sup> and R<sup>8J</sup> are independently selected from the group: 1) hydrogen, 2) hydroxy, 3) SO<sub>2</sub>R<sup>9J</sup>, 4) C1-6 alkyl, 5) C1-6 alkoxy, 6) phenyl, 7) naphthyl, 8) furyl, 9) thienyl and 10) pyridyl, wherein groups of 4) — 5) are optionally substituted by one or more substituents independently selected from R<sup>11J</sup>, and groups of 6) — 10) are optionally substituted by one or more substituents independently selected from R<sup>11J</sup> or C1-4 alkyl, R<sup>9J</sup> is selected from the group:

13. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 1, wherein EP<sub>1</sub> antagonist is N-arylsulfonylamide compound of formula (IR)



wherein  $R^{1K}$  is COOH, hydroxymethyl, 5-tetrazolyl, 5-oxo-1,2,4-oxadiazolyl or 5-oxo-1,2,4-thiadiazolyl,  
 $R^{2K}$  is hydrogen, methyl, methoxy or chloro,  
 $R^{3K}$  and  $R^{4K}$  are a combination of (1) methyl and methyl, (2) methyl and chloro, (3) chloro and methyl, or (4) trifluoromethyl and hydrogen; or  $R^3$  and  $R^4$  are taken together with the carbon to which  $R^3$  and  $R^4$  are attached to form (5) cyclopentene, (6) cyclohexene or (7) benzene ring,  
 $R^{5K}$  is isopropyl, isobutyl, 2-methyl-2-propenyl, cyclopropylmethyl, methyl, ethyl, propyl, 2-propenyl or 2-hydroxy-2-methylpropyl,  
 $Ar^K$  is thiazolyl optionally substituted with methyl, pyridyl or 5-methyl-2-furyl,  
 $n^K$  is 0 or 1, with the proviso that when  $R^{1K}$  is 5-tetrazolyl, 5-oxo-1,2,4-oxadiazolyl or 5-oxo-1,2,4-thiadiazolyl, and then  $n$  is 0,  
 an alkyl ester thereof or a non-toxic salt thereof.

14. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 13, wherein  $EP_1$  antagonist is

(1) 4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-5-trifluoromethylphenoxy]methyl]benzoic acid,  
 (2) 4-[2-[N-isopropyl-N-(5-methyl-2-furylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]benzoic acid,  
 (3) 3-methyl-4-[2-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]-4, 5-dimethylphenoxy]methyl]benzoic acid,  
 (4) 4-[6-[N-isobutyl-N-(5-methyl-2-furylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid,  
 (5) 3-methyl-4-[6-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]cinnamic acid,  
 (6) 4-(4, 5-dimethyl-2-[N-methyl-N-(5-methyl-2-furylsulfonyl)-N-propylamino] phenoxy]methyl]benzoic acid,  
 (7) 4-[6-[N-isobutyl-N-(4-methyl-2-thiazolylsulfonyl)amino]indan-5-yloxy]methyl]benzoic acid, a non-toxic salt thereof, or ester thereof.

15. 4-[5-trifluoromethyl-2-[N-(5-methyl-2-furylcarbonyl)-N-isopropylamino] phenoxy]methyl]cinnamic acid or a non-toxic salt thereof.

16. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 1, which comprises a combination of  $EP_1$  antagonist and antianxiety agent.

17. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 1, which comprises a combination of  $EP_1$  antagonist and antidepressant.

18. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 1, which comprises a combination of  $EP_1$  antagonist and anticholinergic agent.

19. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 1, which comprises a combination of  $EP_1$  antagonist and serotonin antagonist.

20. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 1, which comprises a combination of  $EP_1$  antagonist and serotonin agonist.

21. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 1, which comprises a combination of  $EP_1$  antagonist and calcium antagonist.

22. A pharmaceutical composition for the treatment and/or prevention of depression according to the claim 1, which comprises a combination of  $EP_1$  antagonist and phosphodiesterase inhibitor.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP02/02359

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> Int.Cl. <sup>7</sup> A61K45/00, 31/341, 31/426, 31/4402, 31/4406, 31/41, 31/427, 31/4439, 31/4245, C07D307/64, 277/36, 213/71, 403/12, 417/12, 401/12, 413/12, 405/12, A61P43/00, 25/24 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) Int.Cl. <sup>7</sup> A61K45/00, 31/341, 31/426, 31/4402, 31/4406, 31/41, 31/427, 31/4439, 31/4245, C07D307/64, 277/36, 213/71, 403/12, 417/12, 401/12, 413/12, 405/12, A61P43/00, 25/24 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Jitsuyo Shinan Koho 1926-1992 Toroku Jitsuyo Shinan Koho 1994-1996 Kokai Jitsuyo Shinan Koho 1971-1992 Jitsuyo Shinan Toroku Koho 1996-2002 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CA(STN), REGISTRY(STN), MEDLINE(STN), BIOSIS(STN)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 11-322709 A (Ono Pharmaceutical Co., Ltd.), 24 November, 1999 (24.11.99), Par. No. [0007] (Family: none)	1,16-22
A	TAYO, Fola M., Tricyclic antidepressants antagonize prostaglandin(PG) E2-induced contractions of the guinea pig ileum and hypomotility in the mouse, Experientia, 1985, Vol.41, No.4, pages 474 to 476	1,16-22
A	MANKU, M. S. et al., Chloroquine, quinine, procaine, quinidine, tricyclic antidepressants, and methylxanthines as prostaglandin agonists and antagonists, Lancet, 1976, Vol.2, No.7995, pages 1115 to 1117	1,16-22
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "B" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 07 June, 2002 (07.06.02)		Date of mailing of the international search report 25 June, 2002 (25.06.02)
Name and mailing address of the ISA/ Japanese Patent Office		Authorized officer
Facsimile No.		Telephone No.

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP02/02359

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 878465 A2 (Ono Pharmaceutical Co., Ltd.), 18 November, 1998 (18.11.98), Full text & JP 11-29548 A                      & JP 2000-103778 A	2, 3
A X	EP 947500 A1 (Ono Pharmaceutical Co., Ltd.), 06 October, 1999 (06.10.99), Claims; example 59(1) & WO 98/27053 A1	4, 5 15
A	EP 512400 A1 (Searle, G. D., and Co.), 11 November, 1992 (11.11.92), Full text & WO 92/19617 A2	6
A	EP 778821 A1 (Zeneca Ltd.), 18 June, 1997 (18.06.97), Full text & WO 96/06822 A1	7
A	EP 835246 A1 (Zeneca Ltd.), 15 April, 1998 (15.04.98), Full text & JP 11-508878 A	8
A	EP 1071648 A1 (Merck Frosst Canada & Co.), 31 January, 2001 (31.01.01), Full text & JP 2002-506851 A	9
A	WO 00/20371 A1 (Merck Frosst Canada & Co.), 13 April, 2000 (13.04.00), Full text & EP 1119542 A1	10
P, A	WO 01/19814 A2 (Merck Frosst Canada & Co.), 22 March, 2001 (22.03.01), Full text & US 6369084 B1	11
P, A	WO 01/19819 A2 (Merck Frosst Canada & Co.), 22 March, 2001 (22.03.01), Full text & US 6369082 B1	12
A	WO 00/69465 A1 (Ono Pharmaceutical Co., Ltd.), 23 November, 2000 (23.11.00), Full text (Family: none)	13, 14

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